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American Journal  
of Medicine



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# The American Journal of Medicine

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1. Binder, M. J., et al.: *Am. Jour. Med.*, 18:622, Apr., 1955.
2. Sampson, J. J., and Zipser, Albert: *Circulation*, 9:38, Jan., 1954.
3. Nichol, E. S., in Conn, H. F.: *Current Therapy* 1954, Philadelphia, W. B. Saunders Co., 1954, p. 196.
4. Jamison, W. L., et al.: *Jour. Am. Geriat. Soc.*, 3:521, Aug., 1955.
5. Glichrist, A. Rae: *Brit. Med. Jour.*, 2:351, Aug. 16, 1952.

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## C O N T E N T S

## The American Journal of Medicine

Vol. XX MAY 1956 No. 5

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*Clinical Studies*

Functional Evaluation of Mitral Valvulotomy. Superiority of the Treadmill Exercise Tolerance Test to Clinical and Resting Hemodynamic Evaluations in Selecting Patients	R. A. BRUCE, K. A. MERENDINO, J. J. PAMPUSH, G. G. BERGY AND L. L. BROCK	745
The establishment of valid criteria for the selection of patients for mitral valvulotomy depends, in the final analysis, upon the advantages to be gained, over the natural course of mitral stenosis,		

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NEW CONCEPT IN URINE-SUGAR TESTING

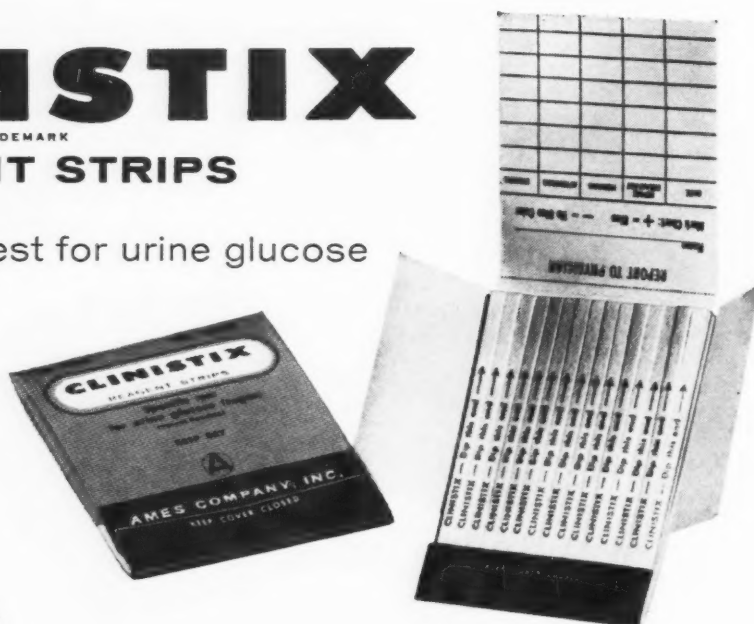
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VOLUME TWENTY

NUMBER FIVE

by surgical intervention. It is becoming increasingly apparent that the first step in such assessment, evaluation of the results of mitral valvulotomy in the individual patient, is no simple matter. The present authors argue persuasively that pre- and postoperative estimates of disability upon exercise, preferably standardized exercise, give better insight into the indications for and results of mitral valvulotomy than do clinical or hemodynamic criteria with the patient at rest. Their convictions are based upon critical and prolonged observation of fifty-two patients before and after mitral valvulotomy. The discussion is interlarded with many incidental comments of interest in connection with the operative procedure.

## Pulmonary Valvular Stenosis with Intact Ventricular Septum. Results of the Brock Type Valvulotomy

C. WALTON LILLEHEI, PAUL WINCHELL, PAUL ADAMS, IVAN BARONOFKY,  
FORREST ADAMS AND RICHARD L. VARCO 756

The authors report a significant fall in mean right ventricular systolic pressure in fifteen of twenty patients with pulmonary valvular stenosis after Brock type valvulotomy; the five failures are presumed to have occurred in patients with undetected infundibular stenosis. Seven of their patients who gave evidence of a right-to-left shunt at the atrial level also showed improvement in arterial oxygen saturation, with a decline in polycythemic response. The results support the usefulness of the Brock procedure, particularly if the surgeon takes the precaution to dilate the valve after incising it.

## A Long-Term Study of the Effect of Crude Rauwolfia Serpentina and of Its Alseroxy-lon Fraction in Patients with Hypertension

ROBERT S. GREEN AND DOMINICK DAVOLOS 760

This detailed and reasonably controlled long-term study of the usefulness and limitations of rauwolfia in the management of essential hypertension confirms the effectiveness of the preparation in a significant proportion of hypertensives and brings out many details of practical value. Of forty patients treated, most of them exhibiting cardiovascular complications, about half responded favorably both objectively and subjectively. The response is usually gradual and slow; therefore an ample trial should be made before the response is finally evaluated. Therapeutic and maintenance dosage must be carefully established for each patient. Side reactions, some already familiar but others not previously described, are discussed in detail, and useful hints concerning them are given. The article as a whole is a substantial contribution to the management of hypertension and deserves close study.

## Therapeutic Activity of Desiccated Thyroid Substance, Sodium L-Thyroxine and D,L-Triiodothyronine. A Comparative Study

THOMAS H. MCGAVACK AND HELLMUTH K. RECKENDORF 774

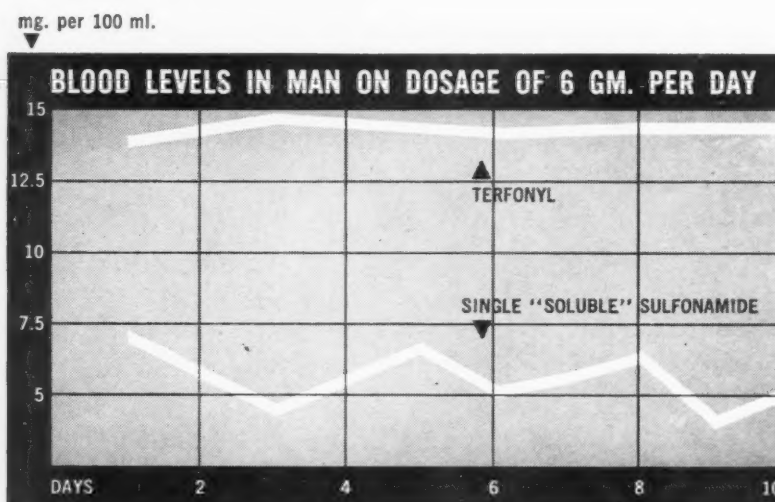
A long term study of the comparative therapeutic efficacy of desiccated thyroid, L-thyroxine and D,L-triiodothyronine in twelve myxedematous subjects. The results are in accord with the general experience that, weight for weight, triiodothyronine is the most effective and rapid agent in restoring the hypothyroid metabolism to normal. Its very potency, however, necessitates special precautions when employed in routine treatment of the myxedematous state.

*Contents continued on page 7*

maximum efficacy with minimum risk

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— After Lehr, D., Modern Med. 23:111 (Jan. 15) 1955.

Terfonyl is absorbed as well as single "soluble" sulfonamides, but is eliminated at a slower rate. For this reason, Terfonyl blood levels are much higher.

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# CONTENTS continued—May 1956

VOLUME TWENTY

NUMBER FIVE

## Seminar on Allergy

- Bronchial Asthma . . . . . FRANCIS C. LOWELL 778

All too often the important and vexing problems of bronchial asthma are considered either solely from the classic viewpoint of the allergist or only as an abstract abnormality in pulmonary dynamics. Dr. Lowell has admirably fused these two points of view into one organic whole, successively considering asthma in terms of impaired patency of the airway and the anatomic and functional consequences thereof; then in terms of experimental induction in the susceptible patient, and the significance of such observations; and finally enlightened analysis of allergic and related causes, with concluding remarks on the principles of management. Study of this article will give better insight into the nature of bronchial asthma.

## Case Reports

- Potassium Depletion by Enemas . . . . . MARCELLE F. DUNNING AND FRED PLUM 789

It has been appreciated for some time that significant potassium depletion may occur as a result of protracted excess loss of gastrointestinal fluids, from both the upper and lower ends of the intestine; this is in fact made use of in the emergency management of hyperkalemia. The present study makes clear that protracted use of prolonged enemas may have as a consequence undesirable and indeed dangerous potassium depletion. The points made have considerable practical significance and should be given attention.

## Scleroderma of the Kidneys

- CHARLES A. HANNIGAN, MARGARET HOPKINS HANNIGAN AND EDWIN L. SCOTT 793

While sclerodermatous involvement of the kidney is a well recognized complication, this report cites many interesting and informative details.

## Congenital Hemorrhagic Diathesis of the Prothrombin Complex

- T. NEWCOMB, M. MATTER, L. CONROY, Q. B. DEMARSH AND C. A. FINCH 798

In a report of unusual interest, the authors describe a thirty-two year old patient who since early childhood suffered recurring hemorrhages at varying sites. After much confusion in diagnosis, she was finally found to have what appears to be a congenital deficiency of prothrombin and factor VII, coagulation defects similar to those produced by dicumarol.

## Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism

- A. L. FREEDMAN, P. S. BARR AND E. A. BRODY 806

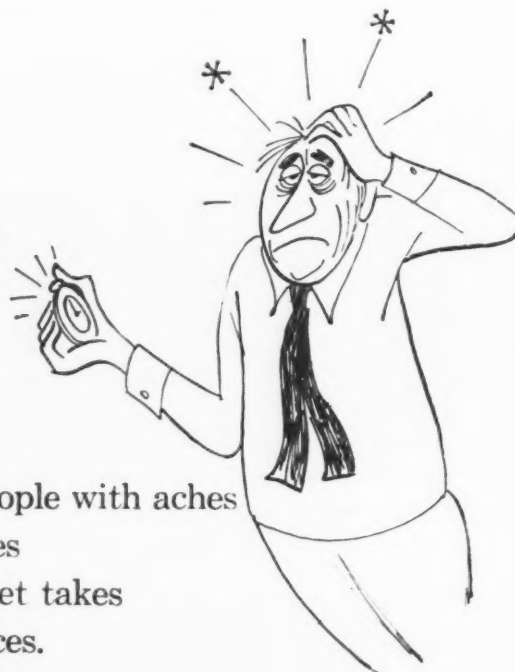
While studying retraction of the blood clot in a patient in whom thrombocytopenic purpura developed following administration of quinidine, the authors noted hemolysis in the tube to which quinidine had been added to the patient's blood. This stimulated further investigation of the hemolytic anemia along the lines of Ackroyd's analysis of thrombocytopenic purpura due to sedormid hypersensitivity. The outcome was an elegant demonstration, in the patient in question, of a specific antigen-antibody reaction resulting in hemagglutination and hemolysis, but only when the responsible drug, quinidine, was present.

*Advertising Index on 3rd cover*

*Change of address must reach us one month preceding month of issue.*

## GOT A STOP WATCH?

Verse by  
RICHARD ARMOUR  
Illustrations by  
LEO HERSHFIELD



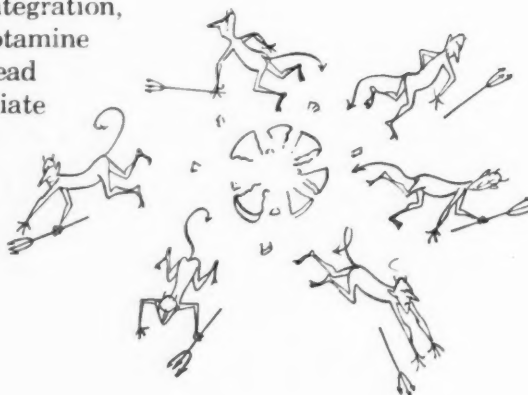
One thing that's important for people with aches  
As awful as migraine produces  
Is the time that the rescuing tablet takes  
To dissolve in the gastric juices.

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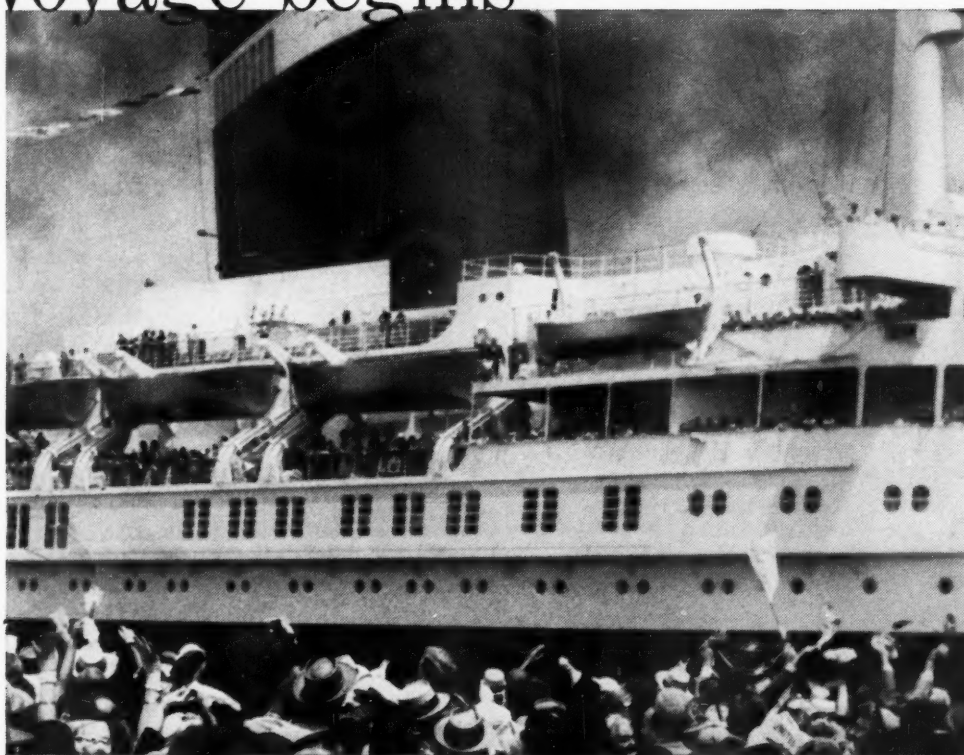
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1. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755 (March 3) 1956. \*Trademark



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9/12/55

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\*Communication to Abbott Laboratories

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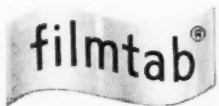
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Dihydrostreptomycin	14.2	25.9	12.5	38.7	27.2	28.0	6.6
Antibiotic B	3.5	0	0	66.1	63.6	0	2.2
Penicillin	3.5	0	0	27.4	39.3	0	0
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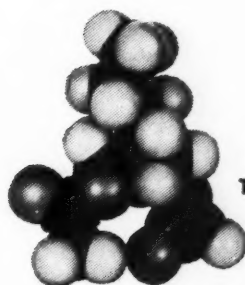
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REFERENCES: 1. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 2. Perry, R. E., Jr.: North Carolina M. J. 16:567, 1955.

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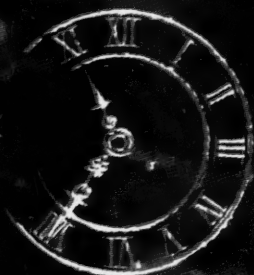
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1. Eisfelder, H.W.: *Am. Pract. & Dig. Treat.*, 5:778 (Oct.) 1954).

2. Sebrell, W.H., Jr.: *J.A.M.A.*, 152:42 (May, 1953).

3. Sherman, R.J.: *Medical Times*, 82:107 (Feb., 1954).

Write for  
60-10-70 Menu pads, weight charts,  
and samples of Obedrin.

THE S. E. MASSENGILL COMPANY  
BRISTOL, TENNESSEE



*forecast:*

**picnics  
and  
pollen**

*time for*

**Tyzine<sup>®</sup>**  
brand of tetrahydrozoline hydrochloride



*for relief of allergic nasal congestion in minutes for hours*

**Supplied:**

TYZINE Nasal Solution, 1-oz. dropper bottles, 0.1%. Nasal Spray, 15 cc., in plastic bottles, 0.1%. Pediatric Nasal Drops, 1/2-oz. bottles, 0.05%, with calibrated dropper for precise dosage.

**Note:** As with certain other widely used nasal decongestants, overdosage may cause drowsiness in infants and children. Although no effect on blood pressure has been reported, it is recommended that caution be observed in treating hypertensive or hyperthyroid patients.

1. Pace, W. G.: *Mil. Med.* 118:34, 1956.
2. Graves, J. W.: *Eye, Ear, Nose & Throat Month.* 34:670, 1955.
3. Menger, H. C.: *New York J. Med.* 55:812, 1955.

When hay fever and other seasonal allergies have a field day, remember the "superior"<sup>1-3</sup> decongestive properties of TYZINE... effective immediately and lasting up to 6 hours or longer after a single application... odorless, tasteless... free of sting, burn, irritation and rebound congestion.



**PFIZER LABORATORIES**  
*Division, Chas. Pfizer & Co., Inc.*  
Brooklyn 6, New York



# New ganglionic blocker lowers blood pressure consistently, predictably, usually with just 2 oral doses per day

Patients with moderate to severe essential hypertension, and even with malignant hypertension, often respond satisfactorily to a ganglionic blocking agent such as Ecolid. It can be used alone or — for maximal control of blood pressure with minimal side effects — in combination with other antihypertensive agents such as Serpasil or Apresoline.

## Advantages

Ecolid has the following advantages over other ganglionic blockers:

- long action, usually requires only two oral doses per day
- rapid absorption — promptly reduces systolic and diastolic pressures
- consistent and predictable response — smoother control
- lower dosage required than with other ganglionic blockers
- minimal likelihood of drug tolerance

## Clinical observations

In a study of four ganglionic blocking agents, Winsor<sup>1</sup> found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson<sup>2</sup> reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.<sup>2,3</sup>

*For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."*

## References:

1. Winsor, T.: Am. J. M. Sc. 230:133 (Aug.) 1955.
2. Grimson, K. S.: J.A.M.A. 158:359 (June 4) 1955.
3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation 11:733 (May) 1955.
4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology 6:507 (Dec.) 1955.
5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955.
6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. 2:1189 (Nov. 12) 1955.

SUPPLIED: ECOLID Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).

DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

Ambulatory patients			Hospitalized patients		
DAY	A.M.	P.M.	DAY	A.M.	P.M.
1	25 mg.	—	1	50 mg.	—
2	25 mg.	25 mg.	2	50 mg.	50 mg.
3	50 mg.	25 mg.	3	100 mg.	50 mg.
4	50 mg.	50 mg.	4	100 mg.	100 mg.
5	75 mg.	50 mg.	to optimal response		
6	75 mg.	75 mg.			
7	100 mg.	75 mg.			
8	100 mg.	100 mg.			

SERPASIL® (reserpine CIBA)

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)

ROTCOCOTES T-™ (dry-compressed, coated tablets CIBA)

# Ecolid<sup>T.M.</sup>

chloride

(chlorisondamine chloride CIBA)

## REPRESENTATIVE CLINICAL STUDIES OF **Ecolid**\*

Number of Patients	Initial Oral Dosage	Responses	Duration of Action	References
59 (Total Series)	75 to 300 mg. daily	Compared with other ganglionic blockers, small doses of Ecolid were employed and greater hypotensive effect was obtained. Rapid absorption and long duration of hypotensive action.	Postural hypotension lasted 13.4 hours in 5 "test" patients receiving doses of 150 mg.	1
20	50 to 200 mg. daily	Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
18	50 to 100 mg. daily	Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
44	50 mg. daily	35 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
12	25 to 200 mg. daily	Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

\*To date, a total of 63 investigators have reported on the use of Ecolid in more than 500 patients. They were practically unanimous in the opinion that Ecolid was highly effective. Nearly all commented on the prolonged duration of action—about 8 to 12 hours—which permitted a twice daily dosage schedule in most cases.

\*\*Information not available.

SUMMIT, N. J.



Newest in vitamin therapy  
Vitamins as nature intended...

# HOMAGENETS<sup>®</sup>

## THE HOMOGENIZED VITAMINS

For the first time, all the advantages of multivitamin drops are available in a tablet. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form.

As a result of this minute subdivision, the vitamins are absorbed and utilized much more efficiently than those in the usual compressed tablet or elastic capsule.

- Better absorbed and utilized
- Pleasant, candy-like flavor
- No regurgitation, no "fishy burp"
- May be chewed, swallowed, or dissolved in the mouth

Three formulas:

Prenatal  
Pediatric  
Therapeutic

**The S.E. MASSENGILL COMPANY**

Bristol, Tennessee

New York • Kansas City • San Francisco

\*U.S. Patent 2676136





latest  
reported  
findings\*..

additive  
in menopausal relief  
with far fewer  
hormonal side effects  
with androgen-  
estrogen therapy

completely relieved all symptoms in 82 of 101 menopausal patients\*

"...with dosages no greater than one tablet twice a day"\*

avoiding "the principal disadvantage of therapy with estrogens,  
uterine bleeding..."\*

## GYNETONE REPETABS

*Schering*

*for individualized therapy: two strengths*

GYNETONE REPETABS ".02": Ethinyl Estradiol U.S.P. 0.02 mg.  
plus 5 mg. Methyltestosterone U.S.P.

GYNETONE REPETABS ".04": Ethinyl Estradiol U.S.P. 0.04 mg.  
plus 10 mg. Methyltestosterone U.S.P.

GYNETONE,® combined estrogen-androgen.  
REPETABS,® Repeat Action Tablets.

\*Moravec, C. L., and Moravec, M. E.: New York J. Med. 55:2775, 1955.

GT-J-4-456





THE architect who artfully  
the plans for the offices in  
which you are located was not  
completely concerned with how the  
tenant would make use of the space.

That, of course, was left to your  
planning, and only you know enough  
of the "anatomy" of your practice to  
decide which furnishings and instruments  
are needed.

When electrocardiographs and/or  
metabolism testers are considered as  
examining aids, their inclusion in the  
specifications of a plan to build for better  
diagnosis is an important decision.

To help you determine the value of these  
instruments, we will gladly arrange for you  
to include either or both of them in your  
"floor plan" during a *no-obligation-to-you* trial  
period. This will give you an opportunity  
to judge them from your own point of  
view before the final "blueprint" is  
drawn and purchase is made.

When you plan with Sanborn you  
receive extra benefits that can come  
only from a direct-to-user policy. The  
interest in and responsibility towards  
you as the user is with Sanborn Com-  
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Write for descriptive literature  
on the VISO-CARDIETTE  
and/or METABULATOR

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*Sh-hh*

# Placidyl

(ETHCHLORVYNOL, ABBOTT)

*nudges your patient to sleep*  
.....

This gentle new hypnotic *induces* sleep instead of imposing it.

For the many insomnia cases where you may feel barbitu-

rates are not desired. 500 mg. capsules, bottles of 100. *Abbott*



THE  
PATIENT WITH  
SEBORRHEIC  
DERMATITIS  
OF THE  
SCALP

ONLY YOU

CAN GIVE HER RELIEF

...WITH

Selsun<sup>®</sup>

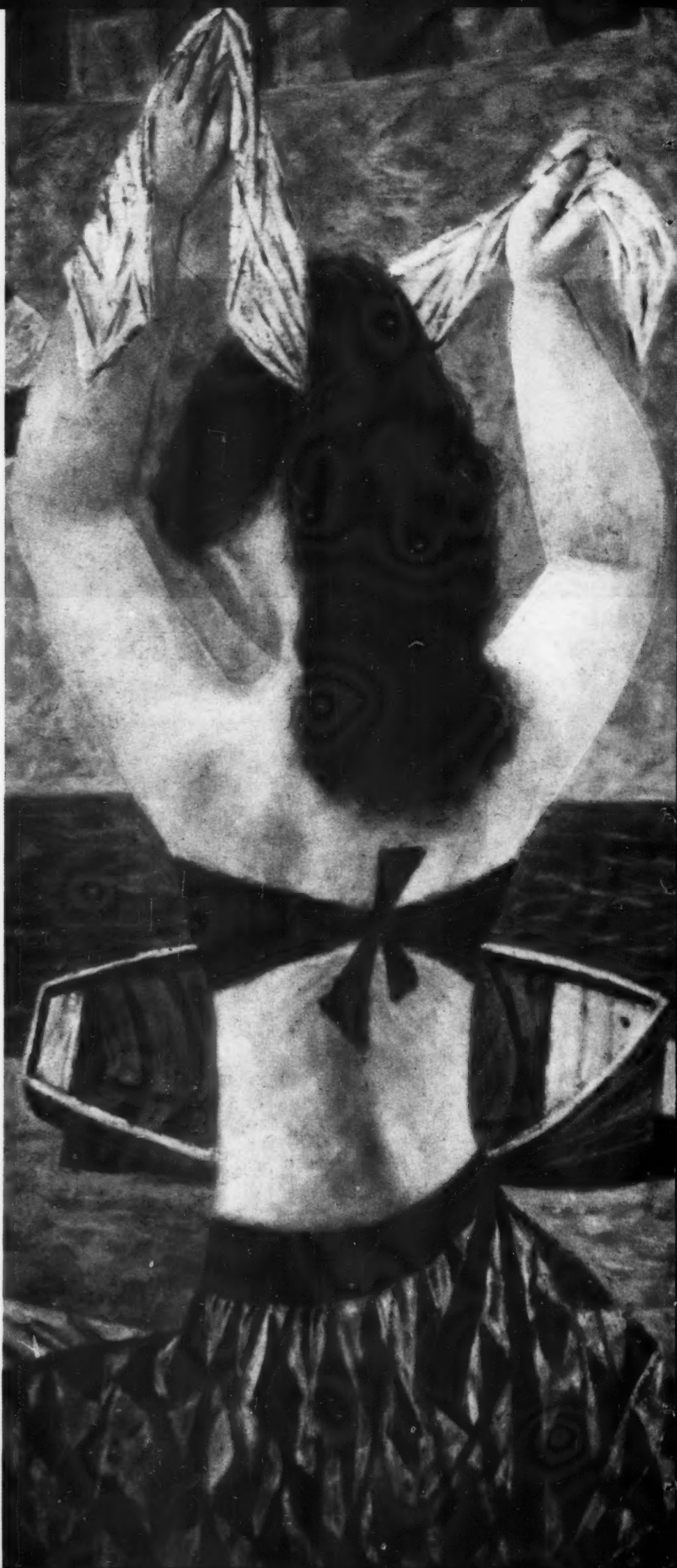
Chances are she has never heard of SELSUN—because it's an ethical prescription product advertised only to the medical profession.


*Yet SELSUN is the most effective treatment for seborrheic dermatitis and dandruff available today.*

When you have occasion to call this condition to patients' attention, and prescribe SELSUN, you're assured of quick, lasting control—in 81-87% of seborrheic dermatitis cases, 92-95% of dandruff cases. Once controlled, SELSUN keeps the scalp healthy up to four weeks between applications.

Simple and pleasant to use as a shampoo, SELSUN is available in 4-fluidounce bottles with directions. **Abbott**

<sup>®</sup>Selenium Sulfide, Abbott





## **XYLOCAINE® HCl SOLUTION ASTRA**

**The Name That Marks a New Era in Local Anesthesia**

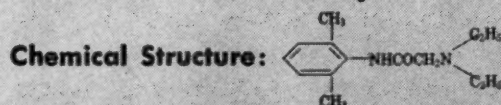
Xylocaine provides peak values in:

- Duration • Clinical Effectiveness • Clinical Tolerance • Speed
- Stability • Versatility • Clinical Predictability • Safety • Depth

Trade Name : XYLOCAINE

Generic Name : lidocaine\*

Chemical Name:  $\alpha$ -Diethylaminoaceto-2,6-xylidide



Potency : Two to three times that of procaine.

Duration of Action : Two to three times that of procaine.

Anesthetic Index : 1.8.

Surface Anesthetic Index : 8.

Safety Factor : Two to three times that of procaine (because smaller concentrations and volumes are clinically as effective).

Sensitivity : Allergic manifestations and sensitizing reactions have never been reported.

Inhibition of Therapeutic Action of Sulfonamides or Antibiotics : None.

Versatility : Effective in local infiltration anesthesia; in major conduction anesthesia; in temporary therapeutic blocks for relief of pain; in topical anesthesia.

Available on Request : Descriptive literature, bibliography, and trial supply.

Supplied : Vials, 0.5%, 1% and 2% in 20 cc. and 50 cc. without and with epinephrine 1:100,000; 100 cc. vials, 1% without epinephrine.

Ampoules, 2 cc., 2% without and with epinephrine 1:100,000.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass.

\*U. S. PATENT NO. 2,441,498







**the point is this...**

## **HydroCortone®-T B A**

(HYDROCORTISONE TERTIARY-BUTYLACETATE, MERCK)

*gives the arthritic patient more days of freedom  
from joint symptoms—in many patients the  
anti-rheumatic effect persists 2 to 10 times longer  
than after injection of hydrocortisone acetate.  
Its action is local and without systemic effect.*



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**SUPPLIED:** SALINE SUSPENSION HYDROCORTONE-TBA—25 MG./CC., VIALS OF 5 CC.




for  
quicker  
recovery

# STRESSCAPS<sup>\*</sup>

Stress Formula Vitamins Lederle

STRESSCAPS are based on a formula suggested by the National Research Council. They provide adequate vitamin supplementation for patients suffering from prolonged stress—surgery, burns, fractures, trauma or shock.

Stress Formula Vitamins promote wound healing, and stimulate antibody production as well as providing a nutritional reserve of water soluble vitamins.

In  dry-filled sealed capsules (a Lederle exclusive!) for more rapid and complete absorption.

AVERAGE DOSE: 1-2 capsules daily, depending upon the severity of the condition.

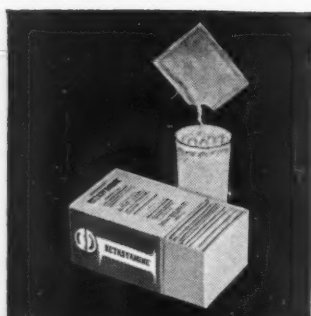
**EACH CAPSULE CONTAINS:**

Thiamine Mononitrate (B <sub>1</sub> )	10 mg.
Riboflavin (B <sub>2</sub> )	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B <sub>6</sub> )	2 mg.
Vitamin B <sub>12</sub>	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.



LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID COMPANY PEARL RIVER, NEW YORK

<sup>\*</sup>REG. U.S. PAT. OFF.



a holiday



# from fatigue

*Betasyamine*<sup>®</sup> . . . for a holiday from fatigue . . . in your "well" patients who feel sick.

*Your tired patients:* Betasyamine has been included in the recovery and rehabilitation programs of many common conditions characterized by chronic fatigue, impaired neuromuscular function, and anxiety tension states. It has been clinically established<sup>1,2,3,4</sup> to be of distinct benefit in relieving exhaustion, re-establishing muscle tone, creating a new mood of optimism. Low energy states have been linked with subnormal muscle and nerve phosphocreatine readings.<sup>1</sup> Betasyamine, containing betaine and glycocyamine, precursors of phosphocreatine, steps up these values to normal, thus tending to restore and maintain the dynamic energy balance.

Containing no unphysiologic sedative or stimulant drug, Betasyamine is true replacement therapy; it offers promise of — a holiday from fatigue — wherever increased burdens and stresses have undermined the energy reserve.

*Average Dosage:* 1 Effervescent Packet; 1 tablespoonful Emulsion; or 5 Tablets three times daily at mealtimes.

*Supplied:* Effervescent Packets (new) — 24's; Emulsion 16 fl. oz.; Tablets — 200's.

*References:* 1. Dixon, H. H., and others: *West. J. Surg.* 62:338 (June) 1954. • 2. Jones, C. H.: (in press). • 3. Watkins, A. L.: *New England J. Med.* 248:621 (April 9) 1953. • 4. Aldes, J. H.: *Bull. Biol. Sciences Foundation* 1:4 (April) 1954.

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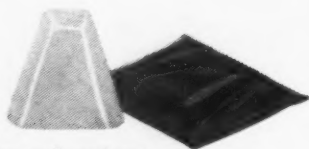
**89.9% of patients  
free from trichomoniasis  
in one menstrual cycle**

*This receptionist's symptoms of local itching and burning are gone, due to her doctor's thorough powder insufflation and her own use of suppositories at home.*

- *many cases refractory to previous therapies responded to TRICOFURON combined therapy in 4 clinical studies of 108 patients.\* Cure rate was 89.9%. Recurrences were few*
- *advantages: contains a specific, trichomonacidal nitrofuran. Kills many secondary invaders but permits essential Döderlein's bacillus to exist. Effective in blood, pus and vaginal debris*
- *office treatment: insufflate TRICOFURON Powder twice the first week and once a week thereafter*
- *home treatment: first week—the patient inserts one TRICOFURON Suppository each morning and one each night at bedtime. Thereafter: one a day—a second if needed—to maintain trichomonacidal action*

Suppositories contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base. Hermetically sealed in green foil. Box of 12. Powder contains 0.1% Furoxone in water-miscible base composed of lactose, dextrose and citric acid. Bottle of 30 Gm.

\*Personal Communications to Medical Department, Eaton Laboratories. Detailed information available on request.



**one cycle regimen**

# TRICOFURON

VAGINAL SUPPOSITORIES AND POWDER

**EATON LABORATORIES, Norwich, N.Y.**



**NITROFURANS**

a new class of antimicrobials  
neither antibiotics nor sulfas





*in pregnancy...a good nutritional start*

**NATABEC® KAPSEALS®**

*vitamin-mineral combination*

Prescribed early in pregnancy, NATABEC Kapseals get your patients off to a good nutritional start—help *keep* vitamin-mineral intake abreast of increased nutritional needs. NATABEC Kapseals provide iron and calcium, as well as important vitamins in a formulation

expressly designed to protect the health of both mother and child.

**DOSAGE:** As a dietary supplement during pregnancy and lactation, one or more Kapseals daily. Available in bottles of 100 and 1,000.



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clinical advantages  
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# TETRACYN<sup>®</sup>

BRAND OF TETRACYCLINE



- rapid absorption and distribution to all parts of the body

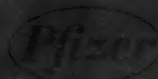
- prompt, broad-spectrum action against infections caused by gram-positive and gram-negative bacteria, spirochetes, certain large viruses and protozoa

- minimal incidence of adverse reactions

- available in a wide selection of convenient dosage forms for oral, parenteral or topical use, including new *faster-acting, better-tasting* **TETRABON<sup>®</sup>** (brand of tetracycline) homogenized mixture, 125 mg. tetracycline in each delicious, fruit-flavored 5 cc. teaspoonful; therapeutic blood levels within one hour. Bottles of 2 fl. oz. and 1 pint, packaged ready to use.

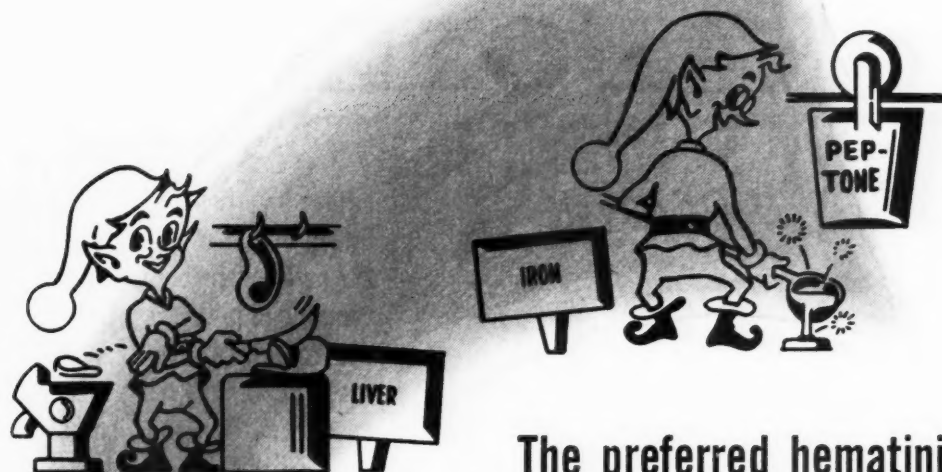
**Tetracycline** the nucleus of modern broad-spectrum activity, discovered and identified by Pfizer scientists

<sup>®</sup>Trademark



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Division, *Chas. Pfizer & Co., Inc.*  
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The preferred hematinic  
with **PEPTONIZED** iron

## LIVITAMIN<sup>®</sup>



Peptonized iron is virtually predigested—better absorbed, better utilized and less toxic than ferrous sulfate. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

*Each fluidounce contains:*

Iron peptonized . . . . .	.420 mg.
(Equiv. in elemental iron to 71 mg.)	
Manganese citrate, soluble . . . . .	.158 mg.
Thiamine hydrochloride . . . . .	10 mg.
Riboflavin . . . . .	10 mg.
Vitamin B <sub>12</sub> (crystalline) . . . . .	20 mcg.
Niacinamide . . . . .	50 mg.
Pyridoxine hydrochloride . . . . .	1 mg.
Pantothenic acid . . . . .	5 mg.
Liver fraction I . . . . .	2 Gm.
Rice bran extract . . . . .	1 Gm.
Inositol . . . . .	30 mg.
Choline . . . . .	60 mg.



### THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

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*blue at breakfast?*

**BONADOXIN<sup>®</sup>**

(BRAND OF MECLIZINE HCl, PYRIDOXINE HCl)

*stops morning  
sickness  
...often "within  
a few hours"<sup>1</sup>*

Fifteen investigators have now confirmed BONADOXIN's efficacy. In 287 patients treated for nausea and vomiting of pregnancy, BONADOXIN was "of great benefit in 90.8% of the cases." Complete relief was often afforded "within a few hours."<sup>1</sup>

Each BONADOXIN tablet contains:

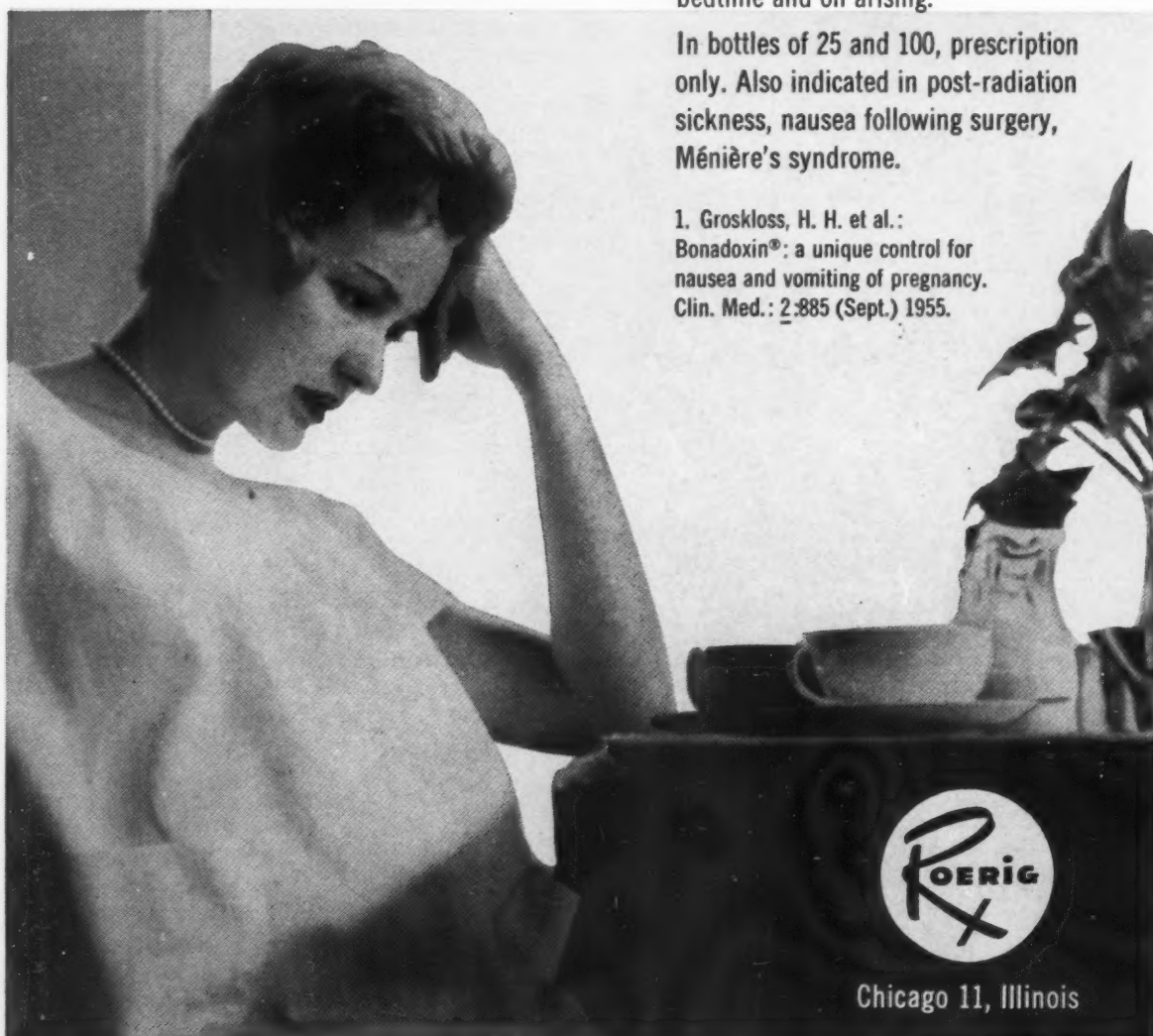
Meclizine HCl . . . . . 25 mg.

Pyridoxine HCl . . . . . 50 mg.

Mild cases: One BONADOXIN tablet at bedtime. Severe cases: One at bedtime and on arising.

In bottles of 25 and 100, prescription only. Also indicated in post-radiation sickness, nausea following surgery, Ménière's syndrome.

1. Groskloss, H. H. et al.: Bonadoxin<sup>®</sup>: a unique control for nausea and vomiting of pregnancy. Clin. Med.: 2:885 (Sept.) 1955.



Chicago 11, Illinois

**For Initial Therapy**

**in Every Case of HYPERTENSION**

# *Rauwiloid*®

**Effective in up to 80% of mild hypertensives<sup>1</sup> and in many patients with more severe forms of hypertension.<sup>2</sup>**

Rauwiloid represents the balanced, mutually potentiated actions<sup>3</sup> of several Rauwolfia alkaloids, of which reserpine and the equally antihypertensive rescinnamine have been isolated.

Hence, reserpine is not the total active antihypertensive principle of the rauwolfia plant.

Rauwiloid is freed of the undesirable alkaloids of the whole rauwolfia root. Recent investigations confirm the desirability of Rauwiloid (because of the balanced action of its contained alkaloids) over single alkaloidal preparations; "...mental depression...was...less frequent with alseroxylon..."<sup>4</sup>

1. Moyer, J. H., in discussion of Galen, W. P., and Duke, J. E.: Outpatient Treatment of Hypertension with Hexamethonium and Hydralazine, *South. M. J.* 47:858 (Sept.) 1954.

2. Finnerty, F. A., Jr.: The Value of Rauwolfia Serpentina in the Hypertensive Patient, *Am. J. Med.* 17:629 (Nov.) 1954.

3. Cronheim, G., and Toekes, I. M.: Comparison of Sedative Properties of Single Alkaloids of Rauwolfia and Their Mixtures, *Meet. Am. Soc. Pharmacol. & Exper. Therap.*, Iowa City, Iowa, Sept. 5, 1955.

4. Moyer, J. H.; Dennis, E., and Ford, R.: Drug Therapy (Rauwolfia) of Hypertension. II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension, *A.M.A. Arch. Int. Med.* 96:530 (Oct.) 1955.

The dose-response curve of Rauwiloid is flat, and its dosage is uncomplicated and easy to prescribe...merely two 2 mg. tablets at bedtime.

Rauwiloid is the original alseroxylon fraction of India-grown Rauwolfia serpentina, Benth., a Riker research development.

**Riker**

LOS ANGELES



for  
profound  
vasodilation  
in acute  
vasospastic  
disorders

**ILIDAR** 'ROCHE'

increases peripheral  
circulation and  
reduces vasospasm by  
(1) adrenergic blockade,  
and (2) direct vasodilation.

Provides relief  
from aching, numbness,  
tingling, and blanching  
of the extremities.

Exceptionally  
well tolerated.

for  
prolonged  
vasodilation  
in chronic  
circulatory  
disorders

**RONIACOL** 'ROCHE'

acts primarily on  
the small arteries  
and arterioles  
to enhance  
collateral circulation.

Especially useful  
for long term therapy  
in older patients

whose feet are  
"always cold."

ILIDAR • BRAND OF AZAPETINE

HOFFMANN-LA ROCHE INC • NUTLEY • N. J.

RONIACOL •  
BRAND OF  
BETA-PYRIDYL CARBINOL

The advertisement features a dark background with two primary graphic elements: a pennant in the upper left and a circle in the lower right. The pennant is black with a white border and contains the text **'TRICOLOID'®\*** in white. The circle is divided horizontally, with the top half black and the bottom half white. The text **'TRICOLOID'®** is in white on the black upper half, and **with PHENOBARBITAL** is in black on the white lower half. To the right of the pennant, the text **TO RESTORE GASTROINTESTINAL TRANQUILLITY** is written in white. To the left of the circle, the text **TO REINFORCE GASTROINTESTINAL TRANQUILLITY WITH LIGHT GENERAL SEDATION** is written in white.

**'TRICOLOID'** or **'TRICOLOID' with Phenobarbital** is indicated, according to the degree of emotional tension which accompanies the symptoms, for the medical management of:

*"lower bowel syndrome,"  
nervous indigestion,  
functional gastroenteritis,  
peptic ulcer*

\***'TRICOLOID'** brand Tricyclamol 50 mg. Sugar-coated tablets

**'TRICOLOID'** brand Tricyclamol 50 mg. with Phenobarbital 16 mg. (gr.  $\frac{1}{4}$ )  
Sugar-coated tablets

Both products in bottles of 100 and 1,000



**BURROUGHS WELLCOME & CO. (U.S.A.) INC.,** Tuckahoe, New York

*Full*  
 ■■■■■■  
*Diuretic Control*  
*with Fewer*  
 ■■■■■■  
*Injections*

The THIOMERIN program combines parenteral and suppository therapy to solve a major diuretic problem—drastic diuresis, patient alternately dry and waterlogged.

Parenteral THIOMERIN initiates diuresis . . . supplemented by THIOMERIN Suppositories to permit maximal spread between injections, to prevent fluid accumulation, and to maintain dry weight. Together, they offer a well-tolerated and convenient regimen for smooth edema control.<sup>1</sup>

Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

1. Daly, J.W.: Am. J. M. Sc. 228:440 (Oct.) 1954.

INJECTION

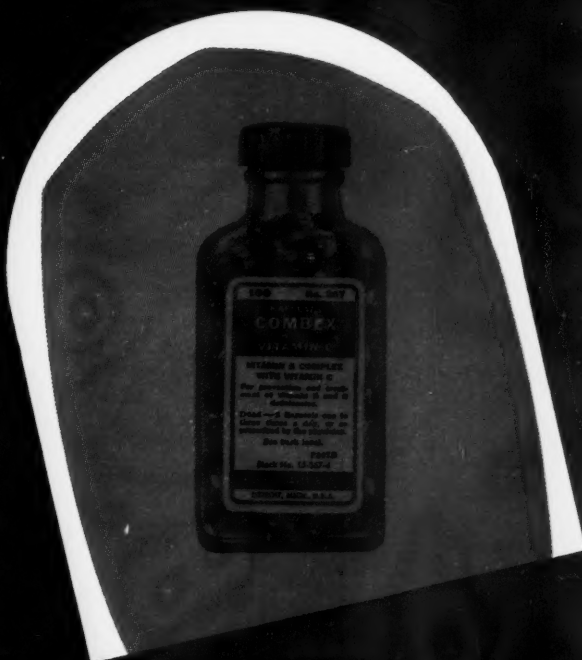
RECTAL SUPPOSITORIES

**THIOMERIN<sup>®</sup>** *Sodium*

MERCAPTOMERIN SODIUM







THE WATER-SOLUBLE VITAMINS  
SO FREQUENTLY NEEDED . . . SO EASILY SUPPLIED

**COMBEX® WITH  
VITAMIN C KAPSEALS®**

Dependable dosage of factors of the B-complex and of vitamin C is assured your patients when you prescribe convenient COMBEX WITH VITAMIN C KAPSEALS.



OTHER VALUABLE MEMBERS OF THE COMBEX FAMILY—

COMBEX KAPSEALS  
COMBEX PARENTERAL

— B-complex factors

THERA-COMBEX® KAPSEALS

— High potency  
B-complex factors and C  
with Taka-Diastase®

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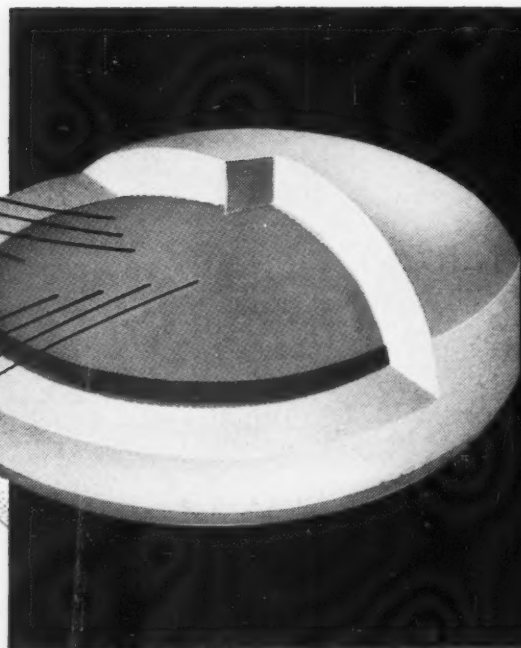
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PARKE, DAVIS & COMPANY · DETROIT, MICHIGAN



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Multiple Compressed Tablets 'CO-DELTRA' and 'CO-HYDELTRA' are unique among the dosage forms of the newer steroids, because they are specifically designed as a tablet within a tablet to provide stability and to release in sequence, antacid and anti-inflammatory agents . . .

1. the outer layer of antacids (aluminum hydroxide gel and magnesium trisilicate) comes into contact with the gastric mucosa first . . . and after it is completely dissolved . . .

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**Multiple  
Compressed  
Tablets**

**'Co-Deltra'**

**Prednisone Buffered**

# benefits of prednisone and prednisolone plus positive antacid action to minimize gastric distress...

A reportedly higher incidence of gastric distress in patients receiving the newer steroids prednisone and prednisolone indicates the desirability of co-administering non-systemic antacids.<sup>1</sup>

To help the physician cope with this problem of gastric distress which might otherwise become an obstacle to therapy with the newer steroids . . . Multiple Compressed Tablets 'CO-DELTRA' (Predni-

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sone Buffered) and 'CO-HYDELTRA' (Prednisolone Buffered) are now available.

'CO-DELTRA' and 'CO-HYDELTRA' are now available in bottles of 30 on your prescription. Each Multiple Compressed Tablet contains:

Prednisone or Prednisolone, 5 mg.; 300 mg. of dried aluminum hydroxide gel, U.S.P., and 50 mg. of magnesium trisilicate.

1. Bollet, A. J., Black, R., and Bunim, J. J.: *J.A.M.A.* 158: 459, June 11, 1955.

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Prednisolone Buffered

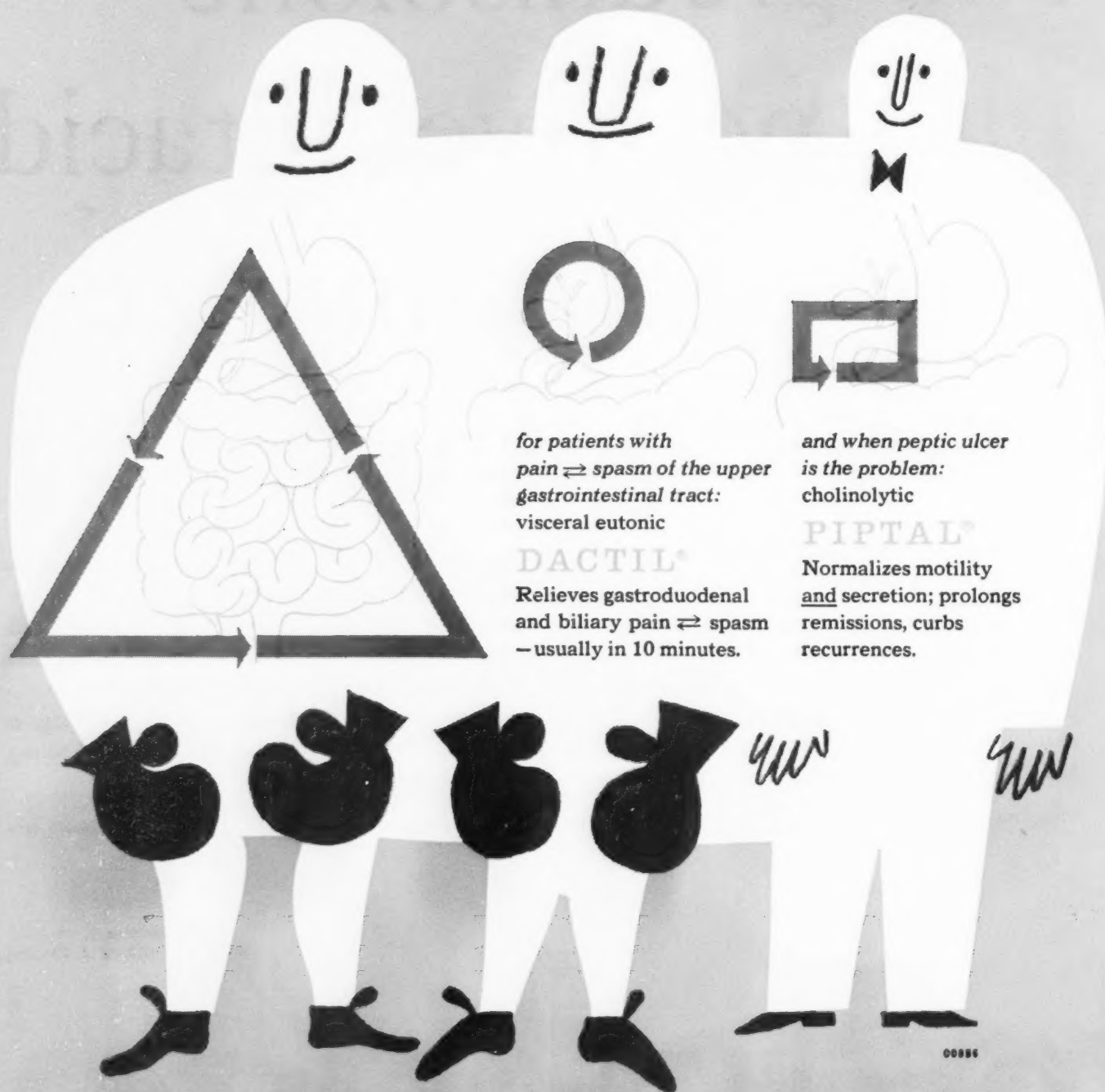


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favorite for generalized G.I. dysfunction

**TRIDAL** paired piperidol action

gives rapid, prolonged relief throughout the G.I. tract



for patients with  
pain  $\rightleftharpoons$  spasm of the upper  
gastrointestinal tract:  
visceral eutonic

**DACTIL**

Relieves gastroduodenal  
and biliary pain  $\rightleftharpoons$  spasm  
—usually in 10 minutes.

and when peptic ulcer  
is the problem:  
cholinolytic

**PIPTAL**

Normalizes motility  
and secretion; prolongs  
remissions, curbs  
recurrences.

Patients on TRIDAL, DACTIL or PIPTAL remain singularly free  
of anticholinergic-antispasmodic side effects.

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a "judicious combination..."

for antiarthritic therapy

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That cortisone and the salicylates have a complementary action has been well established.<sup>1-5</sup> In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."<sup>1</sup>

## INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

## EACH TABLET CONTAINS:

Cortisone acetate . . . . .	2.5 mg.
Sodium salicylate . . . . .	0.3 Gm.
Aluminum hydroxide gel, dried . . . . .	0.12 Gm.
Calcium ascorbate . . . . .	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate . . . . .	60 mg.

\*

U.S. Pat. 2,691,662

BRISTOL, TENNESSEE

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1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. *Clinical Med.* 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in *J.A.M.A.*, 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: *Lancet*, 2:1144 (1954).
5. Spies, T.D., et al.: *J.A.M.A.*, 159:645 (Oct. 15, 1955).

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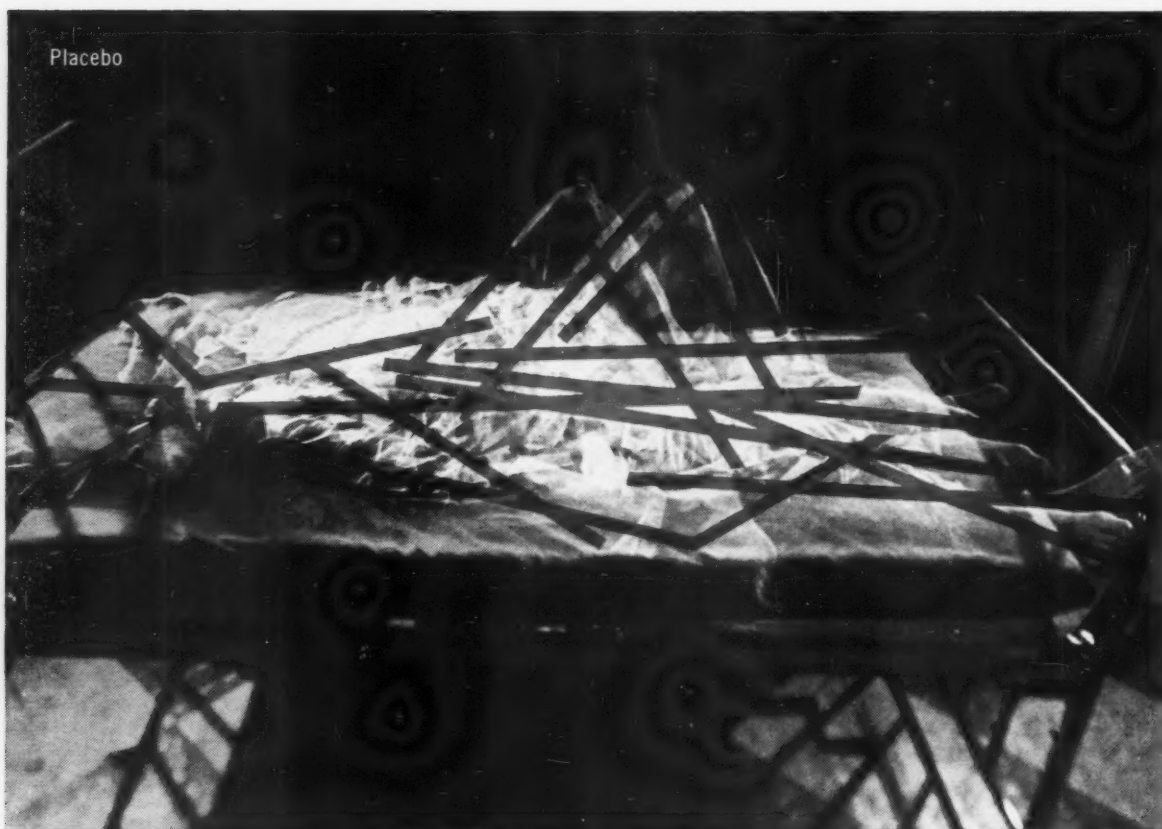
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through-the-night photographs show...

NONBARBITURATE

# Doriden®

Habituation has not been reported

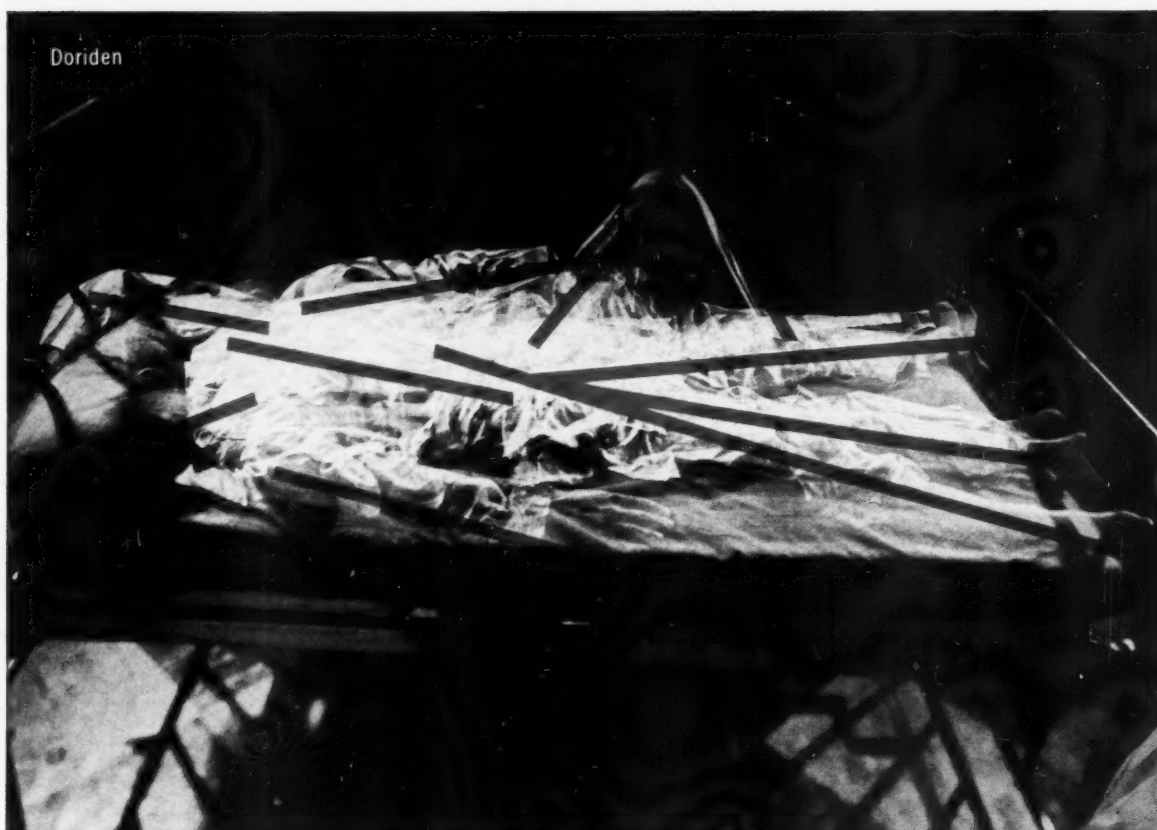


Twenty-eight-year-old male, restless sleeper, tense personality with occasional insomnia, was photographed at fixed intervals during the night to produce a series of exposures on same sheet of film. On placebo (above), unique "stroboscopic" picture shows him in typical fitful night of unrest.

*Further clinical evidence of the sedative  
and hypnotic effectiveness of DORIDEN  
is provided by numerous clinical studies.  
In most cases, Doriden acts in 15 to 30 minutes,  
affords 4 to 8 hours of refreshing sleep...  
and come morning, the patient awakens "clear-headed."*



# induces sound, restful sleep



Same patient on successive night, following administration of Doriden 0.5 Gm. at bedtime, is shown in distinctly more restful repose. Total sleep was achieved in 16 minutes. Close study of activity pattern shows approximately 50 per cent reduction in overt motion and restlessness.

*DORIDEN is also an excellent daytime sedative...  
calms the tense, anxious, overwrought patient.*

DOSAGE: For SLEEP—0.5 Gm. at bedtime.

As a DAYTIME SEDATIVE—0.125 or 0.25 Gm. t.i.d. after meals.

TABLETS, 0.125 Gm., 0.25 Gm. (scored) and 0.5 Gm. (scored).

DORIDEN® (glutethimide CIBA)

**C I B A**  
SUMMIT, N. J.

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for control of fluid balance

By inhibiting carbonic anhydrase, DIAMOX produces prompt, ample diuresis. Taken in the morning, its effect ceases within 6-12 hours thereby permitting uninterrupted sleep at night.

This nontoxic drug—the most widely prescribed of its kind—is particularly suited to long-term use since patients do not readily develop tolerance.

DIAMOX is also effective in the treatment of glaucoma, epilepsy, premenstrual tension, the edema associated with toxemia of pregnancy, and edema caused by certain types of electrolytic imbalance.

250 mg. tablets for oral use  
500 mg. ampuls for intravenous use  
in critical cases

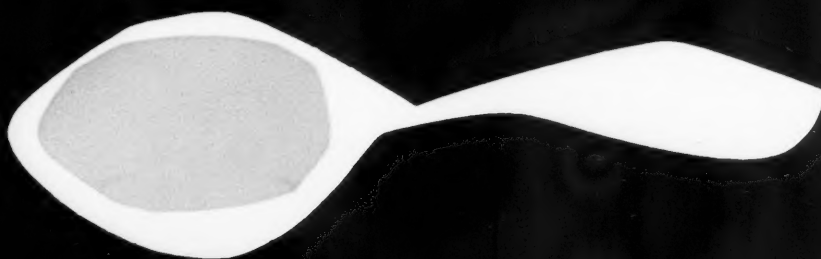
# Diamox\*

Acetazolamide Lederle

the nonmercurial diuretic

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID COMPANY PEARL RIVER, NEW YORK  
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swallowed with a smile

## PALADAC<sup>®</sup>

liquid vitamin supplement

Daily vitamin-taking becomes a pleasant habit for young patients when you prescribe tempting PALADAC. They take to its appealing orange color, aroma, and flavor from the first. PALADAC is popular with mothers, too. It needs no refrigeration, flows evenly, never sticks to the spoon.

Each 4 cc. of PALADAC supplies:

Vitamin A (1.5 mg.)	5,000 units
Vitamin D (25 mcg.)	1,000 units
Vitamin C (ascorbic acid)	50 mg.
Vitamin B <sub>1</sub> (thiamine hydrochloride)	3 mg.
Vitamin B <sub>2</sub> (riboflavin)	3 mg.
Nicotinamide (niacinamide)	20 mg.
Pantothenic Acid (as the sodium salt)	5 mg.
Vitamin B <sub>6</sub> (pyridoxine hydrochloride)	1 mg.
Vitamin B <sub>12</sub> (crystalline)	5 mcg.

**DOSAGE:**

Infants,  $\frac{1}{2}$  teaspoonful daily; children and adults, 1 teaspoonful daily, or as directed by the physician.

**SUPPLIED:**

PALADAC is available in 4-ounce and in 16-ounce bottles.

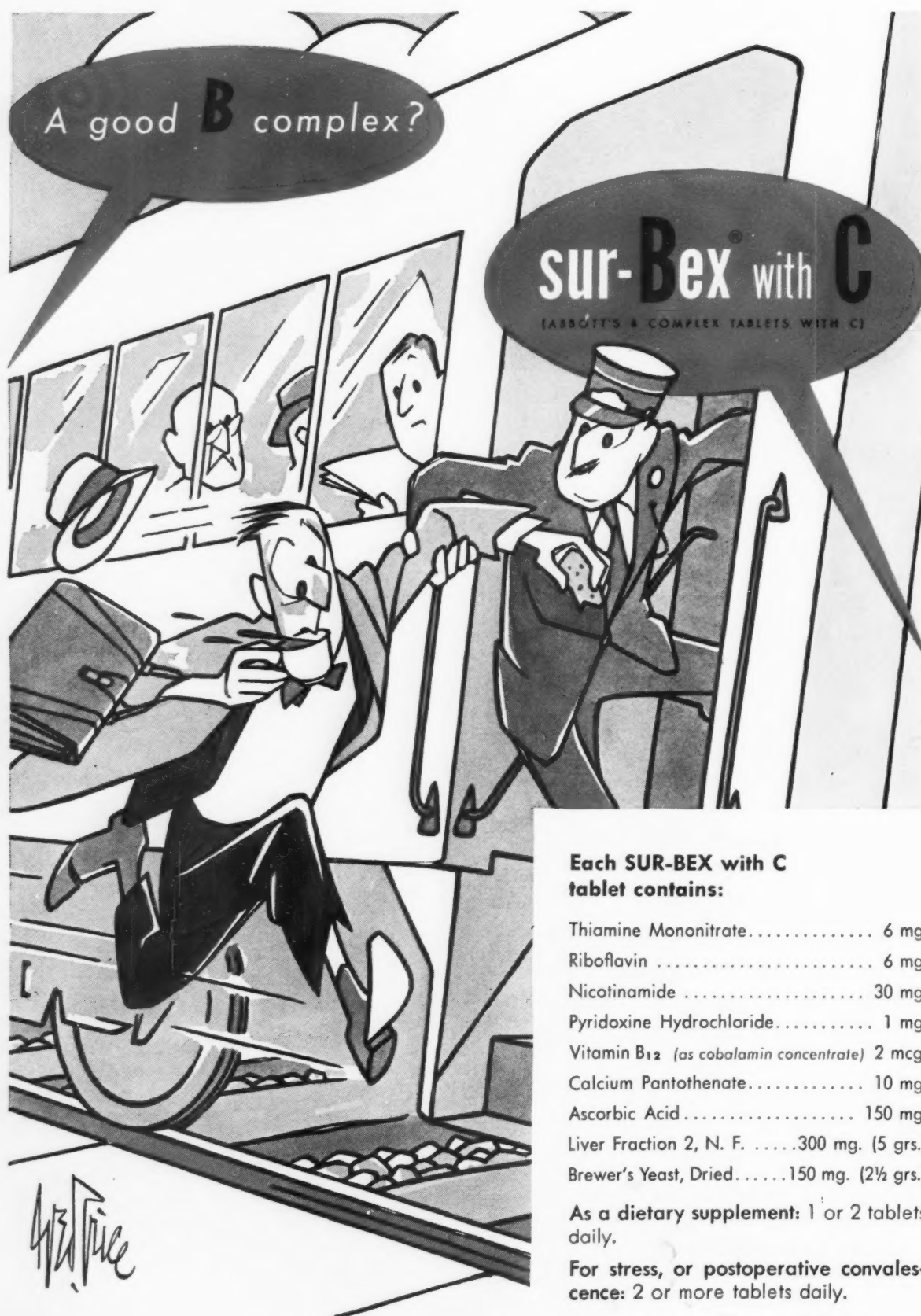
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**Each SUR-BEX with C  
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Thiamine Mononitrate.....	6 mg.
Riboflavin .....	6 mg.
Nicotinamide .....	30 mg.
Pyridoxine Hydrochloride.....	1 mg.
Vitamin B <sub>12</sub> (as cobalamin concentrate)	2 mcg.
Calcium Pantothenate.....	10 mg.
Ascorbic Acid.....	150 mg.
Liver Fraction 2, N. F. ....	300 mg. (5 grs.)
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**As a dietary supplement:** 1 or 2 tablets daily.

**For stress, or postoperative convalescence:** 2 or more tablets daily.

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**Against Pathogen & Pain**  
in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

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Noludar 'Roche' will help  
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barbiturate, not habit  
forming, 50 mg t.i.d.  
provides daytime sedation  
without somnolence,  
while 200 mg h.s. induces  
a sound night's sleep  
without hangover.

Noludar tablets, 50 and  
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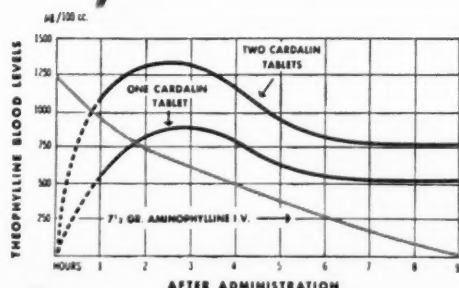
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Noludar®  
brand of methyprylon



**It takes therapeutic blood levels**



*Sustained theophylline blood levels were higher with 1 or 2 oral Cardalin tablets than with 7½ gr. of aminophylline I.V.*

(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

**to produce therapeutic results**

*When the asthmatic gasps for air...*

**Cardalin**

Excellent increases in vital capacity and maximum breathing capacity.

Bickerman, H. A., et al.: Ann. Allergy 11:309, 1953.

Produces productive coughing following bronchodilatation.

Barach, A. L., et al.: Dis. of Chest 23:121, 1953.

Continued relief of paroxysms of bronchospasm.

Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6:399, 1952.

Each Cardalin tablet supplies:

Aminophylline . . . . 5.0 gr.  
Aluminum Hydroxide . . . . . 2.5 gr.

Ethyl Aminobenzoate . . . . . 0.5 gr.

Bottles of 50, 100, 500, 1000.

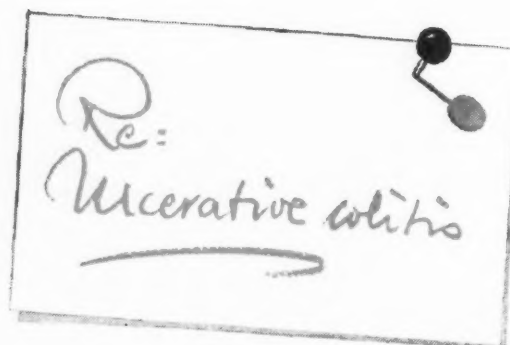
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This is "the most valuable drug that has been introduced for the treatment of ulcerative colitis" in recent years.<sup>1</sup> Results of treatment with Azulfidine "far exceed those of any previous drug used".<sup>2</sup> "It has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."<sup>3</sup>

1. BARGEN, J. A.: "Present Status of Hormonal and Drug Therapy of Ulcerative Colitis", *South. M. J.* 48: 192 (Feb.) 1955.
2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", *Postgrad. Med.* 17: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", *J. A. M. A.* 151: 366 (Jan. 31) 1953.



*Azulfidine*  
BRAND OF SALICYLAZOSULFAPYRIDINE

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in rheumatoid arthritis



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is easier with STERANE<sup>1</sup>—  
3-5 times more active  
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cortisone.<sup>2</sup>

### WALKING

follows rapidly.<sup>1</sup> STERANE  
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of...rheumatoid arthritis.”<sup>3</sup>

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functional mobility is  
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### WITH MINIMAL DISTURBANCE

of electrolyte balance<sup>1-3</sup>—  
patients may even be treated  
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brand of prednisolone

supplied: *White, 5 mg. oral  
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Pink, 1 mg. oral tablets,  
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1. Spies, T. D., et al.: GP 12:73, No. 1,  
1955. 2. Boland, E. W.: J.A.M.A.  
160:613, 1956. 3. Gillhespy, R. O.:  
Lancet 2:1393, 1955.

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*highly effective in monilial infections of the skin*

100,000 units of Mycostatin per gram. 30 Gm. tubes.



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broad spectrum antibacterial therapy  
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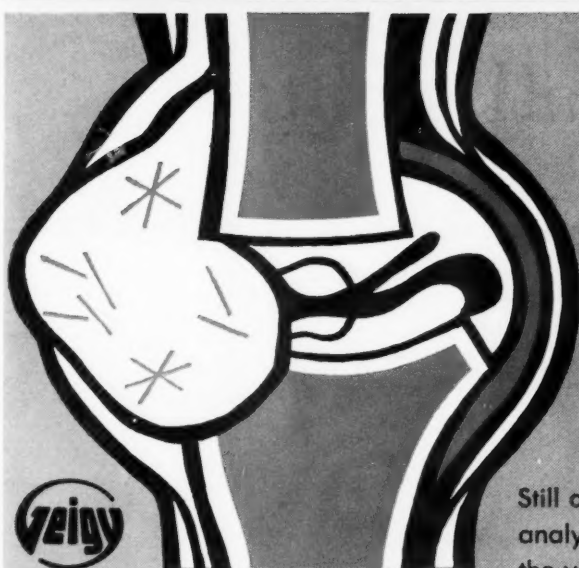
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Still another clinical report, based on a carefully analyzed series of 205 cases, has confirmed the value of BUTAZOLIDIN in arthritis and allied disorders: "Therapeutic effects... are, as a rule, quickly obtained and are easily maintained, and are usually noted within one week."<sup>1</sup>

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1. Denko, C. W.; Ruml, D., and Bergenstal, D. M.: Am. Pract. & Digest Treat. 6:1865, 1955.

2. Holbrook, W. P.: M. Clin. North America 39:405, 1955.

BUTAZOLIDIN® (phenylbutazone GEIGY). Red coated tablets of 100 mg.

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Methscopolamine bromide ..... 2.5 mg.

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The Upjohn Company, Kalamazoo, Michigan





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**MILONTIN<sup>®</sup> KAPSEALS<sup>®</sup> and  
SUSPENSION**

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MILONTIN Kapseals, 0.5 Gm., bottles of 100 and 1,000; also available as MILONTIN Suspension (250 mg. per 4 cc.) in 16-ounce bottles. Detailed information upon request, or from your Parke-Davis representative.

1. Davidson, D. T., Jr.; Lombroso, C., & Markham, C. H.: *New England J. Med.* 253:173, 1955.

2. Zimmerman, F. T.: *New York J. Med.* 55:2338, 1955.



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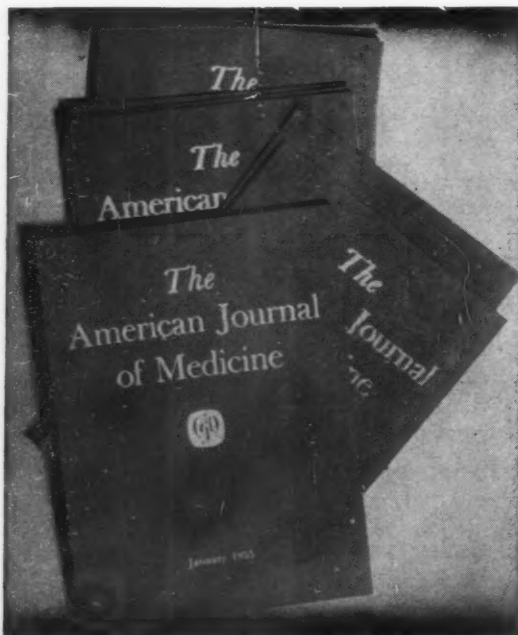
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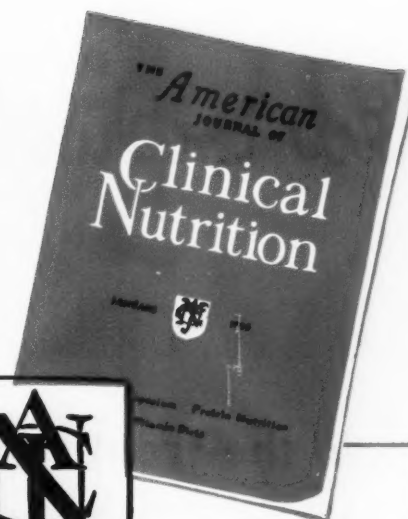
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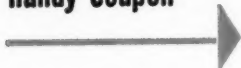
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**ALSO ADDED:** ½ U.S.P. Unit of Vitamin B<sub>12</sub> with intrinsic factor concentrate

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Also available: "Bemotinic" Liquid No. 940—Bottles of 16 fluidounces and 1 gallon.

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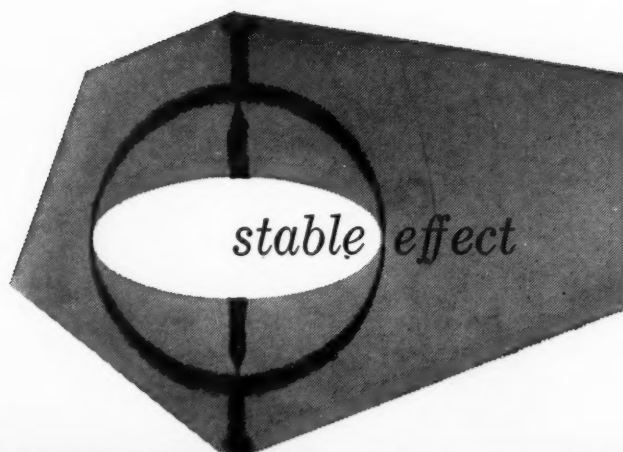
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**in anxiety and tension states . . .**

*stable* ataractic (tranquilizing) effect  
without excessive sedation

**in hypertension . . .**

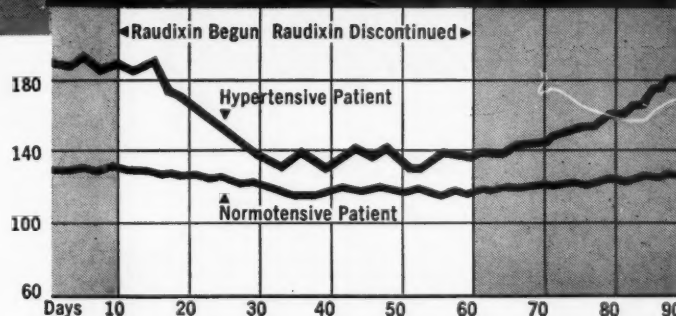
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<sup>1</sup>January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

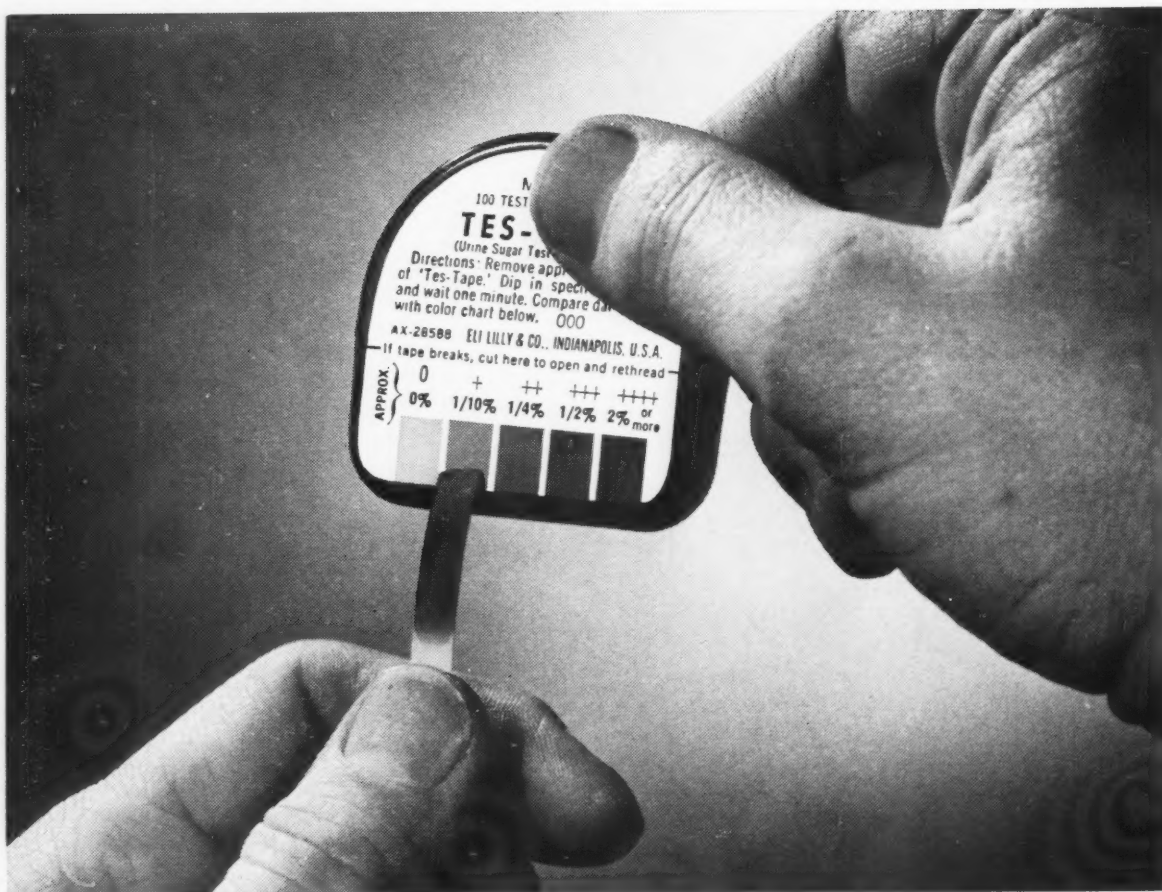


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# The American Journal of Medicine

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## Foreword

IN this issue of *The American Journal of Medicine* is presented a Symposium on The Pathologic Physiology of Thyroid Diseases. The Symposium is designed to summarize modern concepts of normal and morbid physiology of the thyroid gland, with special consideration of the rational management of these diseases.

During the past decade physiologists, biochemists, biophysicists and clinical investigators have pooled their efforts and methods in intensive and imaginative programs of research into the normal and pathologic physiology of the thyroid gland. This recent acceleration in thyroid research can probably be attributed to the fact that modern tools of study have made it possible to approach some previously unanswerable problems with workable methods. The availability of radioactive iodine has made it possible to investigate various functions of the thyroid in physiologic equilibrium. With various chromatographic technics and suitable isotopic labelling methods, it has been possible to identify various iodinated amino acids never before demonstrated in the thyroid gland and in the circulation. By using various goitrogenic drugs which interfere with the production of thyroid hormone, it has been possible to separate and identify certain steps in the synthesis of the thyroid hormones.

Dr. Michel in his review describes, in addition to thyroxine, three other iodinated thyronines which have been identified in both the thyroid gland and the serum of rats; namely, 3:5:3' triiodothyronine, 3:3':5' triiodothyronine and 3:3' triiodothyronine. He also describes pyruvic acid derivatives of triiodothyronine and of thyroxine in the bile, and the acetic acid derivative of triiodothyronine in the kidney. The role

played by each of these iodinated thyronines in the body economy is not yet known. Asper and Wiswell, in their discussion of myxedema, state that triiodothyronine exerts the same qualitative effects produced by thyroxine in myxedematous man. One injection of 3:5:3' triiodothyronine acts much more promptly than does thyroxine. It is more active than thyroxine when used for maintenance therapy. Clarification of the roles of these various compounds and their metabolites in the body economy will await comparative studies in myxedema and cretinism on the various abnormalities of metabolism and growth in these two maladies.

It is quite possible that such studies will reveal that these various iodinated thyronines or metabolites of the thyroid hormones exert metabolic effects on the myxedematous adult or child which differ from those we expect to attain from administration of desiccated thyroid or thyroxine. Evidence for this concept has already been reported by Lerman<sup>1</sup> who observed a loss of weight and a fall in serum cholesterol without a rise in basal metabolic rate in two myxedematous patients treated with moderate doses of 3:5:3' triiodothyroacetic acid. Rall and his associates<sup>2</sup> have observed that a 5 mg. dose of this agent, when administered to a myxedematous man, resulted in a fall in serum cholesterol and a prompt urinary loss of phosphate, nitrogen, sodium and potassium. This dose of "triac" did not cause a significant rise in the rate of oxygen consumption. A single 15 mg. dose of "triac" did, however, cause an increased basal metabolic rate.

Dr. Berson and Dr. Rall have described studies in human subjects in which radioactive iodine and certain anti-thyroid agents were used; these studies have not only complemented observa-

<sup>1</sup> LERMAN, J. and PITT-RIVERS, R. Physiologic activity of triiodothyroacetic acid. *J. Clin. Endocrinol.*, 15: 653-655, 1955.

<sup>2</sup> RALL, J. E., PEARSON, O. H., LIPSETT, M. B. and RAWSON, R. W. The metabolic effects in man of the acetic acid analogues of thyroxine and triiodothyronine. (In press.)

tions made in laboratory animals but have clarified the normal pathways of iodine metabolism in man. Such studies have also helped to clarify certain abnormal states in disease as well as to provide various methods of diagnosing certain states of thyroid disease.

In view of Dr. Sonenberg's reference to an abnormal iodinated protein which has been recovered from the serums of patients who have functioning cancer of the thyroid, we might hope for clarification of qualitative differences in secretory function of some of the benign functioning tumors of the thyroid referred to by Mr. Taylor and Dr. Dobyns.

The concepts of the genesis of tumors of the thyroid gland presented by Mr. Taylor and Dr. Sonenberg would indicate that prophylaxis

for simple goiters may result in a decreased incidence of benign and cancerous goiters.

If one reviews the new knowledge of thyroid physiology so admirably summarized in this issue of *The American Journal of Medicine* and then compares it with the vast number of unanswered questions, satisfaction can be taken from the fact that intensive research in normal and morbid thyroid physiology continues at an accelerated rate. It is hoped that the results of such continued research will lead to further improvement in treating diseased thyroid glands and other diseases of metabolism.

RULON W. RAWSON, M.D.  
*Memorial Center for Cancer  
and Allied Diseases  
New York, New York*



# Symposium on Thyroid Disease

## Pathways of Iodine Metabolism\*

SOLOMON A. BERSON, M.D.

*New York, New York*

SINCE iodine comprises almost two-thirds by weight of thyroid hormone which regulates, in part at least, the metabolic activities of virtually every cell in the animal body, it is not surprising that problems of iodine metabolism† have engaged the attention not only of clinicians, physiologists and chemists but also of physicists and mathematicians. The combined effort of the various investigating disciplines over the past few decades has contributed a truly rewarding body of information bearing on the nature of the iodine-containing substances of the body and on the manner of distribution, transformation and metabolism of these substances.

Although much remains to be explored and probably yet to be discovered, the general scheme of iodine metabolism has been etched out. It may be depicted as a grand cycle (Fig. 1) in which iodide is extracted from the blood by the thyroid gland, is there synthesized into thyroid hormone(s) and stored temporarily in the thyroid follicles, and is then secreted as such into the circulation, from whence it is distributed to the tissues and metabolized; the iodine which is released returns eventually to the plasma as iodide again to be accumulated by the thyroid or excreted, primarily in the urine. Thus the cycle is not a closed one; iodine lost by excretion is replaced by iodine ingested with food and water and the result is a continual turnover of body iodine. The main cycle is also complicated by a number of offshoots and sidings which provide alternative pathways, many details of which still require elucidation.

† Quantitative differences in the various phases of iodine metabolism are frequently observed among different mammalian species. In this review, attention is focused primarily on metabolism in man insofar as quantitative aspects are concerned.

‡ Significant excretion of iodide through any other route but the kidney can be discounted simply on the

### THE IODIDE POOL

A convenient starting point from which to examine the peregrinations of the iodine atom is the iodide pool, since it is this pool from which the thyroid directly derives its iodine supply and which serves as the compartment for exchange of body iodine with exogenous iodine. As already indicated the iodide pool derives its supply from two sources—exogenously from food and water, and endogenously from metabolic degradation of the organic iodine hormone(s) synthesized by the thyroid gland. A variety of incidental sources of iodine such as medications, iodine-containing preparations employed for roentgenologic visualization and so forth also contribute to this pool whether administered by mouth or by parenteral routes. Removal from the iodide pool is effected almost exclusively by the thyroid gland and the kidneys although minute amounts are lost in feces, sweat and milk.‡

The greater part of normally ingested iodine is present as iodide; other forms of inorganic iodine are reduced to iodide prior to absorption into the blood stream,<sup>2</sup> which probably takes place at all levels of the gastrointestinal tract from intact dental enamel<sup>3</sup> to rectum.<sup>4</sup> Iodinated amino acids appear to be well absorbed as such, although once absorbed all but the hormonally active substances are probably degraded rapidly to iodide, as has been demonstrated in the case of diiodotyrosine by Albert and Keating.<sup>5</sup> The kinetics of distribution from the blood stream throughout the iodide pool are best appreciated by following the fate of intravenously administered radioactive iodide. Arterial dilution curves reveal that iodide readily diffuses out of the lung capillaries, and to a slightly greater

observation that 98% of the administered dose of I-131 is excreted in the urine of athyreotic subjects.<sup>1</sup>

\* From the Radioisotope Service, Veterans Administration Hospital, Bronx, N. Y.

## THE IODINE CYCLE

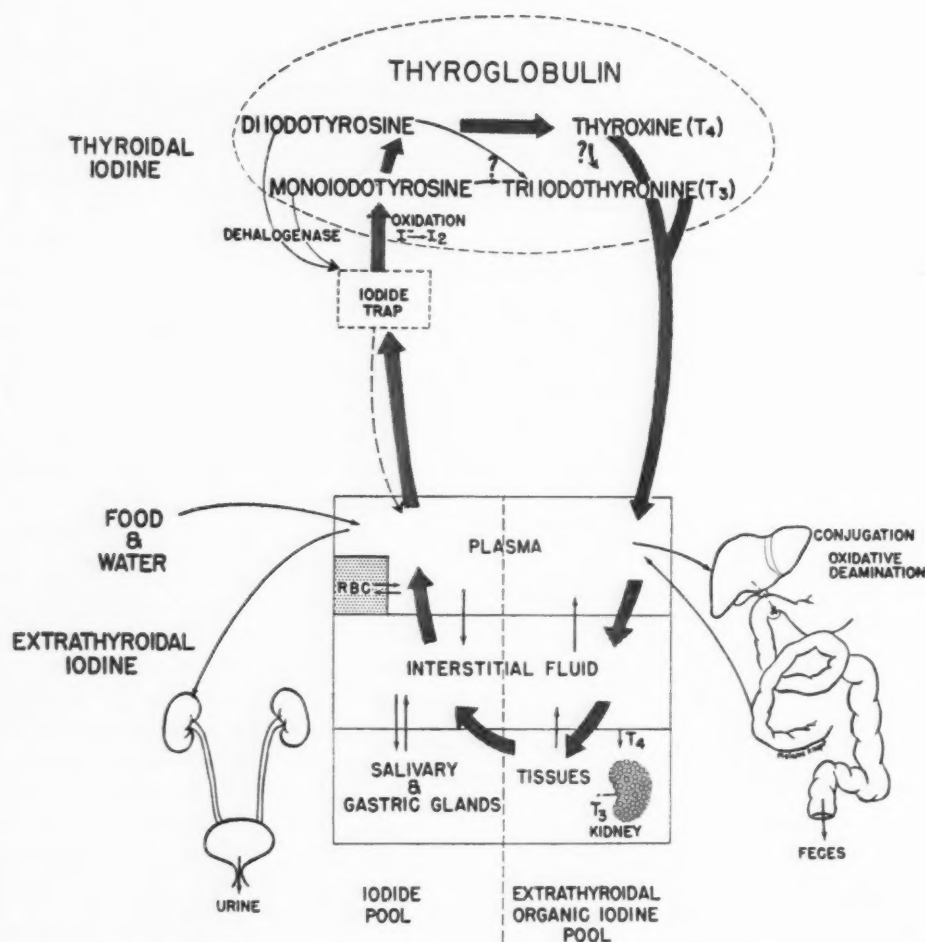


FIG. 1. Schematic model of major pathways of iodine metabolism.

extent than Na<sup>+</sup>, K<sup>+</sup> or phosphate ions,<sup>6</sup> possibly because of concentration by bronchopulmonary epithelium. By the time the first or second circulation through the systemic circuit has been completed the space of distribution is already twice that of the plasma volume<sup>6</sup> and continues to increase rapidly for the first two or three minutes to a value of about 15 per cent of body weight,<sup>7</sup> following which the space expands more slowly to about 26 per cent of body weight by thirty minutes.<sup>7</sup> Distribution is not complete until several hours following injection.<sup>7,8</sup>

Excluding erythrocytes and certain areas of selective concentration, the bulk of the iodide pool may be regarded as coextensive with the extracellular space. However, since the tissue/plasma ratios for chloride are almost identical for most organs<sup>9</sup> and since chloride is more concentrated in the water associated with the matrix proteins of dense connective tissues than in

extracellular water,<sup>10</sup> it is probable that iodide likewise concentrates in these areas. Therefore, primarily because of iodide permeation of red blood cells and concentration in salivary and gastric glands and in dense connective tissue, the ultimate space of distribution of radioactive iodide reaches a value of about 35 per cent of body weight,<sup>7,8,11</sup> which is almost twice the volume of extracellular fluid. The equilibrium distribution of iodide-131 between red blood cells and plasma is attained very rapidly, at least within three minutes<sup>7</sup> and is in the ratio of about 1:1.8,<sup>7,12-15</sup> which is essentially the same as the relative water distribution. Iodide-131 concentration in salivary<sup>8,16,17</sup> and gastric<sup>8,16,18</sup> juices and milk<sup>16</sup> exceeds that of plasma fifteen- to fortyfold. While equilibrium between saliva and plasma is attained within five to ten minutes,<sup>16,17</sup> thirty minutes or more are required for gastric secretions.<sup>16,18</sup>

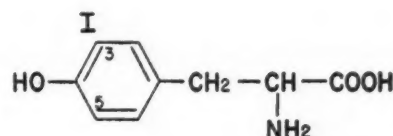
In addition to the capacity to incorporate iodine into organic compounds in the process of hormone synthesis, the normal thyroid gland also has the capacity to concentrate iodide ion, at least to the same degree as salivary and gastric glands. Since, however, under normal circumstances binding of iodide into organic form is so rapid that a significant thyroid/plasma iodide concentration gradient is not achieved, the thyroidal iodide space does not contribute appreciably to the size of the iodide pool. On the other hand, when organic binding is blocked by certain antithyroid agents, the thyroidal iodide space in thyrotoxic subjects may actually exceed, in iodide content, the remainder of the body iodide pool. This function will subsequently be considered in greater detail.

**Removal from the Iodide Pool.** The rate of removal of iodide from the iodide pool depends almost entirely on the rates of excretion into the urine and organic binding in the thyroid. These rates are most meaningfully expressed as renal and thyroidal clearances of plasma iodide,\* as was first demonstrated by Myant, Pochin and Goldie<sup>19</sup> employing I-131 as a tracer. In normal man, values for thyroid clearance obtained in various parts of the world (not regions of endemic goiter) are generally in excellent agreement<sup>7, 19-21</sup> with a mean of 17 ml./minute and a range of about 3 to 45 ml./minute. In patients with Graves' disease, clearances range from 70 ml./minute to over 1,000 ml./minute. Intermediate values in the range 45 to 70 ml./minute are frequently observed in subjects with inadequately treated Graves' disease<sup>7</sup> or with hyperfunctioning adenomas.<sup>4</sup> The measurement of thyroid clearance has proved to be a valuable laboratory aid in the diagnosis of hyperthyroidism.<sup>7, 19-23</sup>

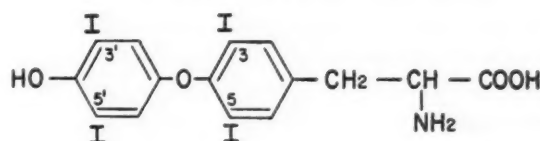
The rates of renal clearance determined by different investigators<sup>7, 19, 24</sup> are also in excellent agreement and indicate a mean value of about 35 ml./minute in normal man. Unlike the thyroid clearance, which is sensitive to change in the plasma concentration of iodide, the renal iodide clearance is constant over all ranges of iodide concentration examined.<sup>25</sup>

Total clearance from the iodide pool is therefore normally effected at a rate of about 50 ml./minute or 3 L./hour, to which the kidneys contribute about two-thirds and the thyroid

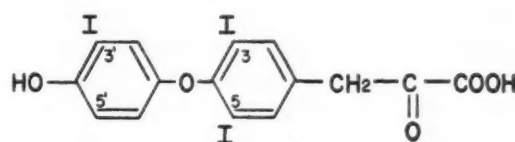
about one-third. Taking a value of 25 L. for the pool size, the rate of turnover is then about 12 per cent per hour, which is in good agreement with measurements of the rate constant for turnover of plasma iodide-131 after distribution equilibrium.<sup>26, 27</sup>



3, MONOIODOTYROSINE



3,3',5,5', TETRAIODOTHYRONINE (THYROXINE)



3,5,3', TRIIODOTHYROPYRUVIC ACID

FIG. 2. Some representative compounds of interest in the iodine cycle.

The rate of I-127 accumulation by the thyroid may be calculated from the clearance figures if the plasma concentration of iodide-127 is known. The latter is normally too low for accurate determination by chemical means but Riggs<sup>28</sup> has derived an estimate of 3  $\mu\text{g./L.}$  from the renal clearance of 2 L./hour and the average daily urinary iodide excretion of 150  $\mu\text{g.}$  given by several workers. Concentrations of the same order were estimated by Berson and Yalow<sup>29</sup> from measurements of the hormonal iodine utilization and thyroidal iodide clearance rates, and by Perry and Hughes<sup>30</sup> and Reilly and coworkers,<sup>31</sup> employing the formula of Stanley,<sup>32</sup> which requires the measurement of urinary specific activity following injection of I-131. The product of plasma concentration of iodide-127 and thyroidal clearance rate of iodide-131 thus yields a value of about 75  $\mu\text{g./day}$  for the daily mean normal thyroidal accumulation of iodine. In the presence of low plasma iodide levels, as in iodine-deficient regions, the thyroidal clearance rate increases in order to insure an adequate

\* organ accumulation of iodide per unit time  
plasma concentration of iodide



supply of iodine for hormone synthesis.<sup>33</sup> Low plasma iodide levels resulting from dietary insufficiency are probably also responsible for the high thyroïdal I-131 uptakes observed in alcoholic cirrhosis of the liver.<sup>4,34</sup> The possibility that altered thyrotropin activity is involved in this adaptation is not supported by observations in iodine-deficient rats; these studies reveal an increase in thyroïdal I-131 accumulation within ten days but no increase in thyroid weight until after three to four months of iodine deficiency, at which time serum PBI concentrations also begin to fall.<sup>35</sup> These findings suggest that the thyroid may be autonomous in this response.

Conversely, in the presence of high plasma iodide concentrations, as following ingestion of iodides, thyroïdal I-131 clearance rates are depressed so that iodine accumulation and hormone synthesis are maintained within reasonable bounds. In the case of the normal thyroid, no particular mechanism for this control need be sought since the capacity for synthesis of organic substrates which incorporate iodine is undoubtedly limited, regardless of the amounts of iodine available. However, it has been shown that high serum iodide levels, by producing high thyroïdal concentrations of iodide,<sup>36</sup> actually decrease the absolute amount of iodine bound into organic form.<sup>37</sup> Since this effect is generally only temporary<sup>38</sup> and does not lead to a diminished organic iodine content of the thyroid in Graves' disease, it does not satisfactorily explain the benefits of iodine therapy in this disorder. Yet, in rare cases continued administration of large doses of iodine to euthyroid subjects has resulted in hypothyroidism,<sup>39-41</sup> apparently as a result of persistent inhibition of organic binding of iodine by the thyroid.

The relationship between thyroïdal and renal clearances of plasma iodide deserves emphasis in the interpretation of I-131 tracer tests. Since only the thyroid gland and the kidneys are in competition for plasma iodide, the ultimate accumulation of I-131 by either of these organs, as measured by the twenty-four- or forty-eight-hour thyroïdal uptake or urinary excretion, or both, is simply a reflection of this competition and not a measure of the level of function of either thyroid or kidneys. The high forty-eight-hour thyroïdal uptake of I-131 frequently observed in the presence of renal disease<sup>1</sup> serves as an illustration. If kidney function were completely absent, virtually 100 per cent of administered I-131 would eventually accumu-

late in the thyroid gland despite the fact that, in renal insufficiency, the thyroïdal clearance rates may be even lower than normal owing to chronic iodide retention and consequent elevation of plasma iodide concentrations.<sup>30</sup>

*Endocrine Interrelationships in the Thyroïdal Clearance of Iodide.* Discussion of the effect of antithyroid agents on thyroïdal accumulation of iodide is best deferred to a later section but the influence of some of the other endocrine glands may be mentioned briefly here. The role of the pituitary gland in the stimulation of thyroid function and the reciprocal inhibition which thyroid hormone exerts on the pituitary have been reviewed by D'Angelo.<sup>42</sup> Of interest at this point is the demonstration by Stanley and Astwood<sup>43</sup> that the rate of iodide accumulation by the thyroid is increased within a few hours following the administration of thyrotropin in man. Although the thyroid-stimulating hormone (TSH) of the pituitary gland is capable of accelerating all known thyroid functions concerned with the synthesis and release of thyroid hormone, it should be emphasized that TSH does not produce any qualitative changes in the metabolism of the fully developed thyroid but acts primarily as a regulator for the quantitative control of functions which are autonomous in the thyroid.

Of the other endocrine organs, the influence of the adrenal cortex has been the most intensively studied and the recent availability of adrenal cortical steroids has served to reawaken interest in thyroid-adrenal relationships. Following prolonged treatment with ACTH or cortisone, Wolfson and his associates<sup>44</sup> observed the frequent development of symptoms of hypothyroidism but Hill et al.<sup>45</sup> failed to demonstrate any change in the twenty-four-hour thyroïdal uptake of I-131, although a decrease in the initial rate of iodine accumulation was noted. However, Jacobson and co-workers<sup>46</sup> did observe a definite decrease in I-131 uptake by the thyroid during treatment with cortisone and more extensive studies by Frederickson,<sup>47</sup> and Berson and Yalow<sup>48</sup> demonstrated that large doses of cortisone regularly produced marked inhibition of the iodine-accumulating function of the thyroid gland in man. The renal clearance of iodide-131 was frequently elevated during cortisone therapy<sup>48</sup> but the decreased thyroïdal uptake was not to be explained on this basis since thyroïdal clearances of I-131 were markedly depressed, frequently to hypothyroid levels.<sup>48</sup>

Zingg and Perry<sup>49</sup> also noted that cortisone, and desoxycorticosterone as well, produced a depression of the thyroidal clearance of I-131. It is not known whether the effect of cortisone in man is exerted on the thyroid directly or indirectly through the anterior pituitary. Results of animal experiments have been conflicting and, in any event, are not unreservedly transferable to man because of probable species differences.

#### INTRATHYROIDAL IODINE METABOLISM

Following entry of iodide into the thyroid gland, a complicated chain of reactions ensues by which the inorganic iodide is incorporated into various organic forms. Within the past ten years or so the introduction of various antithyroid substances capable of interrupting the chain at different steps along the pathway and the application of chromatographic analysis to thyroid hydrolysates, with the employment of radioactive iodine as a tracer, have elucidated many of the intermediate reactions. Several of the mechanisms remain obscure.

*Thyroidal Iodide Trap.* Since iodide as such is not reactive with proteins (except in the form of a loose physicochemical ion-protein bond) while, even in the test tube, elemental iodine substitutes readily into tyrosyl residues of peptides and proteins, oxidation of iodide to some such form as  $I_2$  must precede incorporation into an organic form. A block of this reaction appears to have been first demonstrated by Franklin and Chaikoff who observed that surviving thyroid slices, although failing to bind iodide in an organic form in the presence of sulfonamides<sup>50</sup> or thiourea compounds,<sup>51</sup> nevertheless retained the ability to concentrate inorganic iodide. These findings were subsequently confirmed *in vivo*<sup>52-55</sup> and it was shown that the thiouracil-blocked gland could "trap" iodide ion and maintain a concentration several hundred times that in the plasma. When such a block is complete, iodide entering the thyroid gland is observed to be in reversible equilibrium with plasma iodide and, unlike iodine accumulated and bound into organic form by the unblocked gland, can be discharged readily from the thyroid by thiocyanate,<sup>54,56</sup> perchlorate and certain other anions.<sup>57</sup> The designation "trap" is therefore somewhat misleading, since in these characteristics iodide concentrated by the thyroid does not, in fact, differ fundamentally from that part of the iodide pool which resides in the salivary and gastric glands. However, be-

cause of the subsequent fate of thyroidal iodide and the tremendously high iodide concentration gradient which can be maintained by thyroid over plasma, the thyroid trap has a position of special interest. In an effort to elucidate the mechanism by which the thyroid gland concentrates iodide ion, the kinetics of the trapping process have been studied by several workers employing I-131.<sup>58-61</sup> Under the influence of blocking agents of the thiouracil or mercaptoimidazole series, administration of I-131 is followed by an accumulation of radioactivity in the thyroid which soon reaches a peak and, with attainment of equilibrium, then declines parallel to the plasma concentration of I-131.<sup>43,55,60</sup> The capacity of the thyroid to concentrate iodide ion may be expressed as the thyroid/plasma iodide concentration ratio or as the "thyroidal iodide space" in liters equivalent of plasma iodide; the latter depends on the size of the gland as well as on the concentration ratio. In thyrotoxic human subjects the concentration gradient may exceed 500:1, the thyroidal iodide space containing as much iodide as 30 to 35 L. of plasma.<sup>60</sup> In the blocked normal thyroid of man the thyroidal iodide space rarely exceeds 400 to 500 ml. plasma<sup>4</sup> but under the influence of thyrotropin an increased concentration gradient is observed within eight to nine hours.<sup>43</sup>

A study of the kinetics of iodide trapping in man<sup>60</sup> indicates that, for practical purposes, transfer of iodide to the untreated gland is a one way passage; binding into an organic form takes place with such rapidity that only negligible amounts of iodide are returned as such from the thyroid trap to the plasma. These conclusions are confirmed by observations that even one or two minutes after I-131 has accumulated within the unblocked gland it is no longer dischargeable by thiocyanate.<sup>60,62</sup> Thus in the unblocked gland a high iodide concentration gradient is not attained, simply because a build up of iodide is prevented by rapid oxidation and incorporation into organic form.

There are special circumstances, however, in which binding is partly inhibited or lacking entirely, even in the absence of specific antithyroid drug therapy. Such deficiency in binding of trapped iodide has been demonstrated in the seven-day chick embryo thyroid<sup>63</sup> and in the glands of certain goitrous cretins.<sup>64</sup> A transient episode of binding block has also been observed following I-131 therapy of hyperthyroidism in man.<sup>60,65</sup>



It has already been noted that certain anions such as  $\text{SCN}^-$  and  $\text{ClO}_4^-$  interfere with thyroidal trapping of iodide. VanderLaan and VanderLaan<sup>64</sup> observed that iodide in large doses also is capable of reducing the thyroid:plasma iodide concentration ratio. Halmi<sup>66</sup> showed that the concentration gradient was inversely related to the plasma concentration of iodide in rats with experimentally induced alterations of thyroid function as well as in normal animals; however, the total amount of trapped iodide increased to a saturation level as plasma iodide levels increased. Wollman and Scow<sup>67</sup> confirmed these findings in mice and concluded that the available data did not permit distinction between an active transport system and a model based on reversible adsorption of iodide to some substance in the thyroid.

Attempts to reproduce the *in vivo* characteristics of the thyroid trap with a cell-free thyroid homogenate have not been successful.<sup>68</sup> Although the functional nature of the trap still remains unknown, it is of considerable interest that radioautographs of trapped iodide-131 show radioactivity distributed throughout the follicles rather than a concentration in cells alone.<sup>69</sup>

*Thyroidal Synthesis of Organic Iodine Compounds.* Since subcutaneous injections of elemental iodine ( $\text{I}_2$ ) are capable of exerting a thyroxine-like action on adrenal size and growth of thyroidectomized animals while similar doses of iodide are virtually without effect,<sup>70</sup> it is evident that the thyroid gland must possess a unique ability to oxidize iodide to  $\text{I}_2$  or some similar reactive form. Astwood<sup>71</sup> has reviewed the evidence suggesting that the oxidation of iodide is catalyzed by a peroxidase, but it is the opinion of Roche and Michel<sup>72</sup> that the presence of a specific oxidase is not physiologically necessary, any system capable of acting on  $\text{I}^-$  under the existing redox potential conditions sufficing. They further indicate that the thyroid follicle shows a lowered redox potential after treatment with thiouracil.

With the formation of elemental iodine, iodination of tyrosyl residues probably occurs almost instantaneously and results in "organic binding" of the iodine. From observations that the capacity of thyroid tissue slices to form diiodotyrosine and thyroxine is greatly reduced when the tissue is minced or mortar-ground and is virtually abolished in homogenized tissue<sup>73</sup> it was concluded that the integrity of the thyroid cell is necessary for the organic binding of iodine. More recently, Weiss<sup>74</sup> has demonstrated

that cellular subfractions of thyroid homogenates (mitochondrial fraction most active), incubated in the presence of tyrosine and copper, incorporate I-131 in the formation of diiodotyrosine and thyroxine even under anaerobic conditions. However, since anaerobiosis and copper are strongly inhibitory to I-131 incorporation by thyroid slices<sup>74</sup> the homogenate system may not reflect *in vivo* mechanisms.

One of the unsolved problems in thyroid physiology is a question of anatomy. Just where does organic binding take place? The most careful anatomic studies employing thin tissue radioautographs have not definitely resolved this problem. Following administration of I-131 to animals with depressed thyroids, Leblond and Gross<sup>75</sup> observed that the earliest localization of protein-bound radioactivity was in the apical portions of the epithelial cells adjacent to the follicular colloid. This deposition produced a ring-like picture in the follicles. Subsequently, the ring autographs spread toward the center of the follicles, radioactivity eventually filling the entire follicular area. In stimulated thyroids, as in animals on a low iodine intake, the earliest radioautographs showed radioactivity only in the colloid.

The report by Doniach and Pelc<sup>76</sup> illustrated similar ring autographs following I-131 administration to thyroxine treated rats; these findings were also interpreted as showing radioactivity in the apices of the cells. In a more recent study by Wollman and Wodinsky<sup>77</sup> radioautographs of normal mice thyroids excised as early as eleven to sixteen seconds, and of normal rat thyroids excised within thirty seconds after I-131 injection, showed protein-bound radioactivity only in the colloid and not in the cells. It is therefore not clear whether the iodinated protein is normally produced in the cells and secreted rapidly as such into the colloid or whether it is produced in the colloid at the cell surface. The demonstration of trapped iodide throughout the follicular lumen<sup>69</sup> and the apparent need for intact cells in the efficient iodination of thyroglobulin<sup>73</sup> are consistent with the hypothesis that the cells secrete thyroglobulin and iodide independently into the follicle but that cellular activity at the apical border is required for oxidation of the iodide and iodination of the adjacent thyroglobulin. Also favoring this sequence is the consideration that if oxidation of iodide occurs within the cells, the cell proteins themselves should successfully compete with thyroglobulin



for the elemental iodine. Furthermore, it has been reported that colloid may continue to form even when iodine incorporation has been blocked with goitrogenic agents.<sup>78</sup> Nevertheless, other leading workers<sup>72</sup> conceive of the iodination process as taking place within the cell, secretion into the follicular lumen resulting only when hormone formation is complete. In either case, most of the organic iodine in the thyroid has been found associated with thyroglobulin, an iodoprotein of molecular weight about 700,000;<sup>79</sup> the relatively small amounts of free iodinated amino acids present are presumed to be derived from the intrafollicular proteolysis of thyroglobulin.

The number of different iodinated amino acids found in thyroid extracts and hydrolysates has been increasing rapidly over the past few years and several others may well have been added to the list by the time this paper appears in print. In 1915 Kendall first reported on the isolation of thyroxine from the thyroid gland and noted its marked potency in the treatment of myxedema.<sup>80</sup> Harington subsequently identified thyroxine as L-3,5,3',5'-tetraiodothyronine<sup>81</sup> and together with Barger<sup>82</sup> synthesized this compound by coupling two molecules of diiodotyrosine. The isolation of diiodotyrosine from the thyroid by Harington and Randall<sup>83</sup> in 1929 was confirmed with improved yields by Foster.<sup>84</sup> For almost twenty years thereafter it was believed that diiodotyrosine and thyroxine were the only two iodinated amino acids in the thyroid until the identification of moniodotyrosine with radioactive iodine by Fink and Fink<sup>85</sup> in 1948. The identification of L-3,5,3'-triiodothyronine in plasma and thyroid, its extraction from the thyroid gland and its hormonal activity were reported in a brilliant series of papers by Gross and Pitt-Rivers in 1952 and 1953.<sup>86-90</sup> It was shown to possess a greater antgoitrogenic<sup>87,90</sup> and calorogenic<sup>88</sup> effect than L-thyroxine. This compound had previously been observed as an unidentified spot on chromatographs of butanol-extracted plasma<sup>91-93</sup> and thyroid homogenates<sup>91</sup> and was also reported to be present in trypsin hydrolysates of thyroid tissue by Roche, Lissitzky and Michel.<sup>94,95</sup> This last group of workers has also identified moniodohistidine in the thyroid to the extent of 2 per cent or less of total thyroidal iodine<sup>96</sup> and more recently Roche and Michel and their co-workers<sup>97</sup> have discovered two new iodinated amino acids in the thyroid gland, L-3,3'-diiodothyronine and L-3,3',5'-triiodothy-

ronine. The former was reported to have an antgoitrogenic activity about 85 per cent that of thyroxine but the latter was relatively inactive. It seems difficult to reconcile the high hormonal activity of the 3,3' derivative with the low activity of the 3,3',5'-triiodothyronine on a structural basis since these findings imply that the iodine atom in the 5 position is unnecessary and that the 5' iodine offers some hindrance to hormonal action; but the latter is not consonant with the hormonal activity of thyroxine. Perhaps the answer lies in a particular attachment to substrates in peripheral cells during deiodination to an hormonally active form. (Fig. 2.)

The sequence of thyroxine synthesis has been inferred from results of biochemical syntheses and studies on the rate of incorporation of I-131 into the various thyroidal amino acid residues. Since high specific activities were found earlier in moniodotyrosine than in diiodotyrosine,<sup>98</sup> it appeared that moniodotyrosine was a stable precursor of diiodotyrosine. Similar studies had earlier suggested that diiodotyrosine was a precursor of thyroxine.<sup>99</sup>

The mechanisms of these reactions are still under dispute. It has been proposed that the formation of moniodotyrosine is catalyzed enzymatically by a "tyrosine iodinase."<sup>100</sup> However, in the presence of an oxidase system capable of forming iodine from iodide, specific enzymatic formation of moniodotyrosine would not appear to be necessary in view of the rapidity with which elemental iodine reacts spontaneously with tyrosine in peptide linkage. Of considerable interest is the recent report<sup>101</sup> that stored thyroid slices lose the capacity to concentrate iodide and to form diiodotyrosine or thyroxine but retain the ability to synthesize moniodotyrosine. It was concluded that the mechanisms for synthesis of moniodotyrosine and diiodotyrosine are fundamentally different. However, it is quite possible that the presence of only minute amounts of diiodotyrosine was related to the loss of the iodide-concentrating mechanism, since it is known that moniodotyrosine is found in abundance in slightly iodinated proteins while significant amounts of diiodotyrosine are present only in more heavily iodinated proteins.<sup>102</sup>

There have been several other attempts to implicate specific enzymatic participation in the iodination of moniodotyrosine and diiodotyrosine. However, the experimental conditions under which a diminished rate of formation of

one or the other of these amino acids is produced are generally such as to affect also the concentration and/or the oxidation of iodide. There does not appear to be any compelling evidence on which to discard the notion that iodination of tyrosine automatically follows oxidation of iodide. The presence of moniodohistidine in the thyroid,<sup>96</sup> which seems to have no useful purpose, offers further support for this mechanism since moniodohistidine is also found in proteins artificially iodinated with an abundance of iodine.

The suggestion by Harington that thyroxine is formed by the conjugation of two molecules of diiodotyrosine with loss of one alanine sidechain continues to be the favored hypothesis for this synthesis. Although net yields of thyroxine as high as 4 per cent were obtained by butanol extraction of solutions of diiodotyrosine incubated with hydrogen peroxide at 90–100°C. for five hours, the yield was less than 3 per cent after two weeks incubation of diiodotyrosine at 38°C. without added oxidants; the addition of a reducing agent, thiosulfate, suppressed the formation of thyroxine almost entirely.<sup>103</sup> Hence the recovery of thyroxine from artificially iodinated proteins<sup>104</sup> and the demonstration that incubation of acetylated diiodotyrosine derivatives in peptide linkage results in much improved yields of the corresponding thyroxine derivatives<sup>105</sup> has led most workers to regard the condensation reaction as taking place within the thyroglobulin molecule under the influence of some oxidative mechanism, rather than involving the free amino acids themselves. Whether the reaction can be catalyzed alone by the  $I_2$  present in the gland or requires enzymatic action<sup>106</sup> is not clear.

The yield of thyroxine following iodination of proteins appears to depend on spatial relationships between the tyrosine residues and not necessarily on the abundance of tyrosine. Thus Michel and Pitt-Rivers<sup>107</sup> found that, despite the high tyrosine content of silk fibroin, hydrolysis of the iodinated protein yielded only minute amounts of thyroxine. This was thought to be the consequence of steric hindrance by the too closely spaced tyrosine residues. Thyroglobulin does not appear to be particularly adapted for the production of thyroxine. Thyroxine iodine comprises only about 30 per cent of the total organic iodine of the gland<sup>99, 108, 109</sup> and is independent of the amount of iodine present in the thyroid.<sup>109</sup> This proportion was strikingly

constant in all of eleven vertebrate species examined.<sup>110</sup>

The scheme of thyroxine synthesis presented has recently been challenged by the report of Dobyns<sup>111</sup> that  $C^{14}$ -labeled tyrosine, incubated with thyroid gland slices, becomes incorporated into thyroxine but not into diiodotyrosine. It was suggested that diiodotyrosine may be bypassed in the synthesis of thyroxine but it is not clear why the labeled tyrosine was not iodinated independently and recovered as such even if diiodotyrosine is not a precursor of thyroxine.

The synthesis of L-3,5,3'-triiodothyronine has not been clarified. The two most obvious possibilities, deiodination of thyroxine and condensation of L-3,5-diiodotyrosine with L-3-monoiodotyrosine, are considered in detail by Roche and Michel<sup>72</sup> who believe that evidence favoring either pathway is not conclusive.

It is of interest that several years before the discovery of natural L-3,5,3'-triiodothyronine, this compound was tentatively identified by Hird and Trikojus<sup>112</sup> in baryta hydrolysates of iodinated casein. However, since it has been shown by Roche et al.<sup>113</sup> that alkali hydrolysis liberates large amounts of iodide from thyroxine and diiodotyrosine, it is not clear whether triiodothyronine was present in the iodinated protein or appeared as a result of the deiodination of thyroxine. On the other hand triiodothyronine was not detected in baryta hydrolysates of thyroglobulin.<sup>113</sup>

*Release of Thyroid Hormone into the Blood Stream.* The failure to identify thyroglobulin in the serum of normal or thyrotoxic subjects,<sup>114</sup> except following surgical trauma<sup>114</sup> or I-131 induced radiation damage<sup>115–118</sup> to the thyroid, and the subsequent demonstration that the bulk of organic iodine in the plasma is thyroxine in loose combination with plasma proteins<sup>119–122</sup> indicated clearly the role of thyroglobulin as the storage form rather than the circulating form of thyroid hormone. The release of thyroxine into the blood stream requires that the huge thyroglobulin molecule be degraded since it normally is itself apparently unable to pass into the capillaries. A proteolytic enzyme capable of liberating iodinated amino acids from thyroglobulin was indicated in the studies of DeRobertis<sup>123</sup> and has recently been isolated from the thyroid and purified.<sup>124</sup> The absence of significant amounts of moniodotyrosine or diiodotyrosine in the plasma in normal or thyrotoxic subjects<sup>125</sup> may be attributable to rapid destruction in tissues<sup>5, 126</sup> or failure to



be released by the thyroid. The latter possibility is strengthened by the demonstration of a dehalogenating enzyme in thyroid tissue which is capable of removing the halogen from iodinated and brominated tyrosines but not from free 3,5,3'-triiodothyronine or thyroxine or from any of the amino acids in intact thyroglobulin.<sup>127</sup> These studies suggest that only the hormonally active substances are released from the gland whereas the inactive iodotyrosines are deiodinated, the released iodine being reutilized in the biosynthetic pathway. The iodotyrosines therefore act as thyroidal storage forms for iodine in addition to whatever other functions they may serve as steps in the synthesis of hormone. Although rattlesnake venom and thyroid and kidney slices are also capable of deiodinating tyrosine, the reaction in these tissues differs from that in the thyroid dehalogenating system in the appearance of deaminated diiodotyrosine derivatives.<sup>126</sup>

Since 3,5,3'-triiodothyronine is demonstrable in the plasma after administration of thyroxine to athyreotic subjects<sup>92\*</sup>,<sup>128</sup> and is apparently derived from tissue deiodination of thyroxine, as will subsequently be discussed, the finding of small amounts of triiodothyronine in plasma cannot in itself be taken as evidence of its secretion by the thyroid. However, its presence in enzymatic hydrolysates of thyroid tissue,<sup>89,95</sup> the failure to demonstrate its inactivation by thyroid dehalogenase<sup>127</sup> and the appearance of I-131 labeled triiodothyronine prior to the appearance of labeled thyroxine in the plasma of thyrotoxic subjects<sup>129</sup> indicate that it is secreted by the thyroid, at least in small amounts.

The thyroidal secretion of thyroxine appears to be under the regulatory control of the pituitary. By blocking thyroidal reutilization of I-131 with 1-methyl 2-mercaptoimidazole (tapazole®), Goldsmith, Stanbury and Brownell<sup>130</sup> demonstrated that the increased rate of loss of thyroidal I-131 following thyrotropin administration in man was attributable to an increased rate of thyroid hormone secretion independent of any effect on the iodine accumulation process or on hormone synthesis. The rate of thyroid hormone secretion was studied quantitatively in normal and thyrotoxic human subjects by Berson and Yalow.<sup>29</sup> Following the administration of I-131, a constant ratio of thyroidal I-131 to plasma organic I-131 was generally attained within a few weeks. The conclusion that specific activities

\* Compare with ref. 86.

in thyroid and plasma were essentially identical after this time was supported by the maintenance of a constant specific activity in the plasma protein-bound iodine during marked depletion of thyroidal and plasma hormone stores induced by tapazole administration. It was therefore possible to evaluate *in vivo* the quantity of organically bound I-131 in the thyroid from measurements of thyroidal radioactivity and plasma specific activity. The "exchangeable thyroidal organic iodine pool" was found to contain from 5 to 20 mg. of iodine, which is in agreement with values obtained by direct chemical analysis of thyroid tissue.<sup>108,131</sup> Significantly smaller amounts (as low as 800 µg.) were observed in patients treated for Graves' disease by surgical or radioiodine ablation and in those whose thyroids were depleted by anti-thyroid drug therapy. The rate of thyroidal secretion of I-131 was calculated from the loss of I-131 from the gland after the administration of tapazole to block reuptake of I-131 and also from the kinetics of distribution of thyroidal I-131 into the extrathyroidal pool prior to tapazole administration. Values obtained by both of these methods were generally in good agreement and indicated rates of secretion as high as 10 per cent per day of total thyroidal iodine in thyrotoxic subjects. Thyroid hormone secretion was then calculated from the product of the rate of thyroidal secretion and the amount of organic iodine in the thyroid. Euthyroid subjects secreted approximately 115 to 120 µg. organic iodine per day while values in thyrotoxic subjects reached as high as 1,000 µg. per day.<sup>29</sup>

#### THE EXTRATHYROIDAL ORGANIC IODINE POOL

Following secretion into the plasma, the thyroid hormones are distributed to the tissues where they may undergo several different types of chemical transformation before or after being partially or completely deiodinated. The ultimate fate of thyroxine and triiodothyronine has been approached from two different aspects—the over-all rate of metabolic degradation of the iodine moiety to inorganic iodide and the specific metabolic alterations which take place in the various tissues.

*Distribution and Over-all Rate of Degradation of Thyroid Hormones.* Investigations of the distribution and metabolism of the hormonally active substances have employed hormones labeled with I-131 biosynthetically (*in vivo*) as well as *in vitro* labeled synthetic thyroxine and triiodo-



thyronine. Since the latter generally contain the radioactive label in the 3',5' positions which have been reported to be more labile than iodine atoms in the 3,5 positions,<sup>132</sup> the results of studies utilizing synthetic and biosynthetic labeled substances may not be directly comparable. Thus Myant and Pochin<sup>133</sup> observed a much more rapid disappearance from plasma of synthetic L or D,L radiothyroxine (labeled in the prime positions) than of transfused plasma hormone labeled *in vivo*. However, this rapid disappearance of synthetic thyroxine (also labeled in the prime positions) was not observed by Sterling and co-workers<sup>134</sup> whose data showed rates of disappearance of the same order as that observed by Berson and Yalow<sup>29</sup> employing biosynthetically labeled hormone. Sterling et al.<sup>134</sup> noted in euthyroid subjects that L-thyroxine was distributed into an apparent volume of about 8 to 9 L. over a period of two to three days after intravenous injection, following which it disappeared from the blood stream at a rate of about 11 per cent per day. Triiodothyronine disappeared at a significantly faster rate averaging 27.4 per cent per day. The volume of distribution of triiodothyronine has not been reported. In view of the different rates of metabolism of these two hormonally active amino acids, both of which are known to be present in plasma, information on the rate of metabolism of *in vivo* synthesized hormones would appear to be desirable. In the few reports<sup>29,133,135,136</sup> which have dealt with the metabolism of transfused biosynthesized hormone, observations did not extend beyond the mixing period in the majority of cases. In one study, however, labeled plasma from a thyrotoxic patient was transfused into euthyroid, hyperthyroid and hypothyroid subjects and observations were made for a period of nine to eleven days.<sup>29</sup> Distribution into a volume of 8.7 to 11.2 L. was essentially complete within about forty-eight hours and the subsequent rate of turnover depended on the metabolic level of the recipient, being highest in the hyperthyroid subject (22 per cent/day) and lowest in the hypothyroid subject (9.8 per cent/day). Labeled hormone disappeared from the blood stream of the euthyroid subject at a rate of 12.4 per cent/day. The rate of metabolism has also been evaluated from the plasma clearance of hormone labeled endogenously<sup>29,137</sup> by the prior administration of I-131. In this case the rate of deiodinative metabolism of hormone is calculated from the urinary excretion of I-131 after reutilization

by the thyroid is blocked with antithyroid drugs<sup>29</sup> or is calculated, in the absence of such block from the urinary excretion of iodide-131 and the thyroidal urinary iodide-131 accumulation ratio.<sup>29,137</sup>

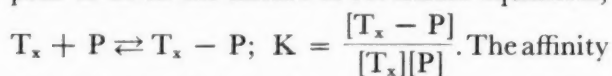
While available data for the rates of metabolism of synthetic thyroxine and biosynthetic hormone in euthyroid man are insufficient to justify a statistical comparison, it does appear that the biosynthetic hormone is degraded at a slightly faster rate. This difference is resolved when account is taken of the fact that biosynthetic hormone in plasma also contains small amounts of triiodothyronine which is much more rapidly degraded than thyroxine.<sup>134</sup>

Since the rate of metabolism of thyroid hormone, like the rate of metabolism of other body constituents, appears to depend on the general state of metabolism, it is meaningless to discuss the biologic half-time of thyroid hormone without reference to the metabolic level. Riggs<sup>28</sup> has calculated the daily hormone utilization rate from data on the serum protein bound iodine concentrations achieved at various daily dose levels of desiccated thyroid and has demonstrated an increasing rate of utilization with increase in plasma hormone concentration. These data and those of Berson and Yalow<sup>29</sup> employing hormone labeled endogenously with I-131 indicate that the amount of hormonal iodine utilized daily in man can be quantitatively expressed by the formula  $D = 2.9(PBI)^2$ , where D is micrograms hormonal iodine degraded daily and (PBI) is micrograms protein bound iodine per 100 ml. plasma. Thus the fractional rate of hormone metabolism  $\left(\frac{D}{(PBI)}\right)$

is proportional to the serum protein bound iodine concentration. It will be of interest to observe whether or not a similar dependency on the serum PBI obtains with the rate of metabolism of other hormones. In a recent study by Peterson and associates<sup>138</sup> the rate of metabolism of hydrocortisone was about twice normal in two of three thyrotoxic subjects and half of the normal rate in two or three patients with myxedema.

*Thyroxine Binding to the Serum Proteins.* It has already been mentioned that thyroxine is carried in the plasma in loose combination with the serum proteins. It has also been shown by zone electrophoresis<sup>139-141</sup> that, in physiologic concentrations, the bulk of thyroxine is bound to a protein migrating between the  $\alpha_1$  and  $\alpha_2$  proteins ("interalpha" region); the remainder is bound

to serum albumin. The reactions between thyroxine ( $T_x$ ) and the serum proteins (P) appear to be in the nature of reversible equilibria,



The affinity of the interalpha protein for thyroxine is greater than that of serum albumin but at high thyroxine concentrations the thyroxine binding sites on the interalpha protein approach the saturation level and a greater fraction of the thyroxine binds to the albumin. Triiodothyronine also binds to the interalpha protein but less strongly than thyroxine and is readily displaced by thyroxine.<sup>142</sup>

**Tissue Metabolism of Thyroid Hormones.** Since the initial rate of disappearance from the blood stream of I-131 labeled thyroxine and triiodothyronine as well as of endogenously labelled hormone is considerably faster than has been demonstrated with the serum proteins, it appears likely that the unbound hormones pass through the capillaries into the tissues. Since the interstitial fluids also contain serum proteins, it is to be expected that the rapidity with which the hormones can exert an action on cells *in vivo* must be limited at least by the dissociation constant of the  $T_x - P$  complex in plasma and tissues. Thus Barker and Klitgaard<sup>143</sup> noted a latent period of more than six hours for the metabolic action of D,L-thyroxine on all tissues after subcutaneous injection into hypothyroid rats. The more rapid metabolism of triiodothyronine than of thyroxine *in vivo*<sup>134</sup> may be partly related to its less firm binding to plasma and tissue proteins. However, there is also the possibility that thyroxine itself is not hormonally active as such but is converted in the tissues to an active form. Peripheral deiodination of thyroxine to triiodothyronine is evidenced by the appearance of labeled triiodothyronine in the plasma following the injection of labeled thyroxine to athyreotic human subjects.<sup>128</sup> Furthermore, the appearance of an unknown iodinated compound (subsequently identified as triiodothyronine\*) in the plasma of thyroidectomized mice given I-131 labeled thyroxine had previously been noted by Gross and Leblond.<sup>92</sup> In support of these observations, Albright and Larson and their co-workers have demonstrated deiodination of thyroxine to triiodothyronine *in vitro* by rat kidney slices<sup>144</sup> but not by other tissues except cardiac muscle.<sup>145</sup> The rate of deiodination was dependent upon

the level of tissue metabolism, being greatest in slices taken from hyperthyroid animals and slowest in slices removed from hypothyroid animals;<sup>145</sup> this is in agreement with observations on the over-all rate of utilization of thyroid hormone *in vivo*.<sup>28,29</sup> Since boiling of the kidney slices for five minutes destroyed thyroxine deiodinating activity, participation of an enzyme was postulated.<sup>145</sup> However, MacLagen and Sprott<sup>146</sup> have reported deiodination of thyroxine by homogenates of a number of rat tissues, particularly liver, and these systems required two hours boiling at 100°C. for complete inactivation. There may be several different types of deiodinating systems which are revealed under different experimental conditions.

Also pertinent to the identity of the active tissue form of thyroid hormone is the observation that, although increased metabolic activity of tissues removed from animals treated with thyroid substances has been noted frequently, direct addition of thyroxine or triiodothyronine to surviving tissue *in vitro* does not accelerate oxygen consumption;<sup>147</sup> yet both hormones are effective in stimulating  $O_2$  uptake by a rat heart homogenate-cytochrome-succinate system.<sup>147</sup> The recent report by Thibault and Pitt-Rivers<sup>148</sup> that the addition of tetraiodothyroacetic acid or triiodothyroacetic acid produces an immediate rise in  $O_2$  consumption of isolated kidney slices has suggested that this compound might be the active form of thyroid hormone. Although oxidative deamination and decarboxylation followed by oxidation of the terminal carbon atom to the corresponding thyroacetic acid derivatives (alanine side chain replaced by acetic acid) has not been demonstrated, there is evidence to support the importance of the first of these steps in the metabolism of the iodinated amino acids. The demonstration of a deaminative step preceding deiodination was first reported by Foster and Gutman,<sup>149</sup> who isolated 3,5-diiodo-4-hydroxyphenyl-lactic acid from the urine of rabbits fed large amounts of diiodotyrosine. This compound, as well as the corresponding pyruvic acid derivative, was subsequently identified by Tong, Taurog and Chaikoff<sup>150</sup> in the products of metabolism of diiodotyrosine by liver and kidney slices. Following administration of radio-triiodothyronine, radiotriiodothyropyruvic acid has also been detected in bile and urine<sup>151</sup> which further suggests that deamination may precede deiodination of thyroid hormones *in vivo* and that the initial degradative steps may be similar

\* Compare with ref. 86.



to those of the oxidative metabolism of other amino acids.

An anatomic site of hormone localization within the cell has not been established. Cellular subfractionation of liver homogenates showed no particular concentration of radioactivity in nuclei, mitochondria or microsomes over a three-day period following injection of I-131 labeled L-thyroxine in rats with ablated thyroids.<sup>152</sup> However, no evidence was presented that all or any of the radioactivity in these homogenate fractions was still in the form of thyroxine.

*Enterohepatic Cycle and Fecal Excretion.* In 1947 Gross and Leblond<sup>153</sup> showed that the liver and gastrointestinal tract of the rat concentrated large amounts of I-131 labeled thyroxine, following injection of radiothyroxine. They found, by ligation of the bile ducts and exclusion of various parts of the gastrointestinal tract, that although small amounts of thyroxine passed directly into stomach, jejunum and colon, excretion in the bile accounted for the major portion of intestinal thyroxine. Biliary excretion of radiothyroxine in the dog and rat was confirmed by Taurog, Briggs and Chaikoff<sup>154</sup> who also observed another radioactive compound, later identified as the glucuronide of thyroxine.<sup>155</sup> The presence not only of the phenolic glucuro-conjugates of both thyroxine and triiodothyronine<sup>156</sup> but also of the pyruvic acid derivative of triiodothyronine<sup>151</sup> in the bile of rats has been established by chromatographic and specific chemical staining methods by Roche and his associates. The role of the liver in the conjugation of thyroxine, as distinct from its excretory function, was demonstrated by the finding of a conjugated product of radiothyroxine in the bile of a surviving liver preparation after addition of I-131 labeled thyroxine to the perfusate.<sup>157</sup>

Albert and Keating<sup>158</sup> found almost 50 per cent of the administered radioactivity in the liver of the rat one minute after intravenous injection of radiothyroxine. The large amounts which subsequently appeared in the gastrointestinal tract were reduced five- to sixfold by ligation of the bile ducts. Following biliary excretion of thyroxine (in free or conjugated form), however, the greater part must have been reabsorbed through the intestinal wall since radioactivity was secreted into the bowel at a rate of 100 per cent of the injected dose per hour while the rate of excretion in the feces was only 3 per cent/hour, two-thirds of the total radioactivity ultimately being excreted in feces and one-third in urine.<sup>159</sup>

Since the glucuronide of thyroxine, excreted in high concentration in the bile, could not be identified in the plasma,<sup>155</sup> it is likely that it is not reabsorbed as such but is hydrolyzed to free thyroxine by the action of bacterial  $\beta$ -glucuronidase in the intestine.

The magnitude of this enterohepatic circulation of thyroid substances in the rat does not, however, reflect the quantitative disposition of hormone in human subjects. Following biosynthetic labeling of plasma hormone in man by administration of I-131, Berson and Yalow<sup>29</sup> observed that only 10–15 per cent of circulating organically bound I-131 was excreted in the feces, the remainder being excreted in the urine, primarily after metabolic degradation to a non-organic form; the daily fecal clearance of plasma hormone was only about 200 to 450 ml., which is less than 5 per cent of the total extrathyroidal organic iodine pool.<sup>29</sup> That this difference in fecal excretion of rat and man is not attributable simply to differences in the efficiency of reabsorption from the intestine after biliary excretion is indicated by the recovery of only small amounts of hormone from biliary fistulas in man by Johnson and Beierwaltes<sup>160</sup> and by Robbins.<sup>161</sup> It may be concluded, therefore, that the bulk of hormonal iodine in man is ultimately fated for metabolic degradation and return to the iodide pool and that only a small fraction of circulating hormone participates in the enterohepatic circulation.

The iodine cycle has thus made one full turn. A few years hence, no doubt, elucidation of many of the presently unidentified stops in its tour will provide a still more fascinating story of the metabolism of this element.

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#### ADDENDUM

The identification of 3:5:3' labeled thyroacetic acid in the rat kidney following the administration of labeled L-3:5:3'-triiodothyronine was reported recently by Roche, Michel and co-workers (*Compt. rend. de l'Acad. des Sc.*, 241: 1880, 1955). Whether this compound is the "tissue form" of thyroid hormone or simply represents another metabolic product remains a matter of speculation at present.



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# Recent Progress in the Physiology and Biochemistry of Thyroid Hormones\*

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THE discovery of the accumulation of iodine in the thyroid gland has, since the end of the last century, directed research toward the thyroid metabolism of this halogen. About fifteen years ago it was thought that the principal problems of thyroid biochemistry were approaching definitive solution. The nature of iodinated constituents seemed established: thyroglobulin contained thyroxine and 3:5-diiodotyrosine; only the thyroxine possessed hormonal activity, 3:5-diiodotyrosine being its precursor; a satisfactory hypothesis explained thyroxinogenesis.

The large scale use of radioisotopes of iodine, especially I-131, together with the development of more sensitive analytic methods, has shown that the facts are not as simple as was then believed. The discovery of a new iodinated amino acid, 3-monoiodotyrosine, was the starting point of very fruitful research. The presence of new hormones in thyroglobulin has been established and certain mechanisms which lead to secretion of the thyroid hormone(s) have been partially elucidated; the nature of the circulating hormones is better known and knowledge of their metabolism in the peripheral tissues has developed. Elucidation of the biological activities of the hormones, of some of their metabolites, and of a number of structurally related synthetic substances has made substantial progress and hypotheses concerning the active form of the hormones in the end-organ cells have been elaborated.

Only the current aspects of thyroid physiology and biochemistry will be dealt with here. They will be presented in three parts. The first part will include recent research on the nature of thyroid iodine and the process of hormonogenesis. The second will be devoted to recent work dealing with the mechanisms which lead to the secretion of the thyroid hormones and studies on the nature of blood iodine. The third section

will describe the metabolism and the biologic activities of thyroid hormones and of some of their structural analogs.

Numerous general articles on these subjects have been published in recent years,<sup>1-9</sup> as well as aspects of the problem not to be considered in this report. Limitations of space preclude any consideration here of work on the entry of iodine and of some other elements into the thyroid gland and on the general mechanisms of endocrine regulation, embryologic evolution and pathologic manifestations of the thyroid gland.

## NATURE OF THYROID IODINE AND HORMONOGENESIS

*Nature of the Iodinated Constituents of Thyroglobulin.* The thyroid gland is the site of biosynthesis of certain hormones whose essential chemical characteristic is the presence of iodine in the molecule. Reactions preceding hormonogenesis involve, first, the trapping of blood iodide<sup>10</sup> and oxidation of iodide,<sup>11</sup> followed by incorporation of iodine into two amino acids which are constituents of thyroglobulin: tyrosine and histidine.<sup>12</sup> Mono- and diiodotyrosine<sup>13</sup> probably are the precursors of the hormones, while the formation of monoiodohistidine<sup>14</sup> appears to be only a secondary reaction unrelated to hormonogenesis. Thyroxine was the first compound possessing biologic activity to be isolated,<sup>15</sup> identified as to structure and synthesized.<sup>16</sup> It was considered for a long time to be the thyroid hormone but a controversy arose in this connection<sup>17</sup> since thyroxine-containing peptides were as active as the thyroxine itself. This discrepancy can now be explained by the fact that thyroxine is a constituent of a protein, thyroglobulin (in which form it is stored in the gland) and that a thyroid component more active than thyroxine has since been discovered. Traces of thyroxine are also present in the free state<sup>18</sup> but very nearly the

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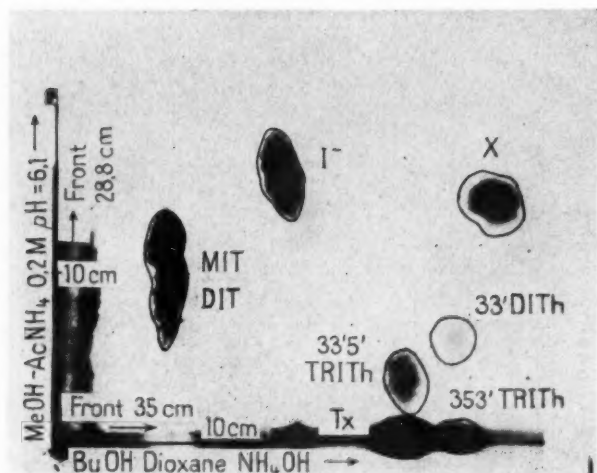


FIG. 1. Autoradiography of a two-dimensional chromatogram of total hydrolysate (pancreatin-papain) of thyroglobulin of rats obtained twelve hours after injection of 50  $\mu$ c. carrier-free radioiodide. X = unknown iodinated substance.

whole of the hormonal iodine is found in the form of protein.<sup>19,20</sup> The precursor iodotyrosines undergo oxidation reactions to give rise to thyroxine. Even before 3:5-diiodotyrosine was isolated and characterized as a constituent of the thyroid gland the hypothesis that thyroxine derived from the condensation of two molecules of 3:5-diiodotyrosine with the loss of one alanine side-chain had been put forward.<sup>16,21</sup> For several years the only experimental basis for this conception was that traces of thyroxine appeared at the end of several weeks of incubation at 37°C. of 3:5-diiodotyrosine in slightly alkaline solution.<sup>22</sup> Study of the biogenesis of thyroid substances was difficult with the methods of investigation then available for under the most favorable conditions the amount of iodine incorporated into thyroglobulin reaches only 1 per cent.<sup>23</sup> When it became possible to establish the kinetics of formation of iodinated compounds in the thyroid gland of animals given radioactive iodide more fruitful research on thyroxinogenesis was feasible.<sup>24</sup> Thus it was shown that monoiodotyrosine is first formed, then the diiodo derivative, and finally thyroxine. Specific activity measurements of the various compounds made at different times support the view that diiodotyrosine is the precursor of thyroxine.

The characterization of 3-monoiodotyrosine in thyroglobulin<sup>25</sup> initiated important progress in the biochemistry of thyroid iodine. It was uncertain at first if this amino acid was a real constituent of the iodoprotein or a product of partial deiodination of 3:5-diiodotyrosine in the

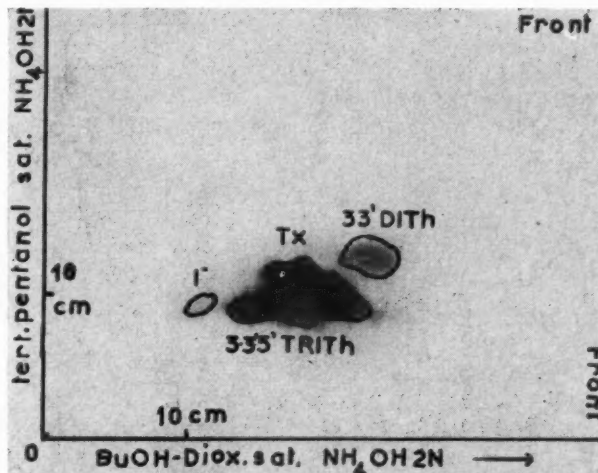


FIG. 2. Autoradiography of a two-dimensional chromatogram of a fractionated proteolytic hydrolysate of the total thyroid gland of rats sacrificed twenty-four hours after injection of 100  $\mu$ c. carrier-free NaI-131.

course of its liberation by alkaline hydrolysis. This uncertainty was removed with the use of proteolytic enzymes, trypsin and papain, for hydrolysis<sup>26</sup> and by identification of 3-monoiodotyrosine in the free form<sup>18</sup> in the thyroid after cathepsin autolysis of thyroglobulin.

The content of 3-monoiodotyrosine in thyroglobulin is relatively high in relation to that of 3:5-diiodotyrosine, especially in the first hours after the administration of radioiodine to animals.<sup>27</sup> It was soon recognized, with the application of chromatography and autoradiography to hydrolysates of thyroid iodoprotein, that the intact protein contained a larger number of iodinated substances than had been appreciated. (Fig. 1.\*) There are at least five unknown substances in the butanol-soluble fraction (free iodinated amino acids), one of which has since been identified as 3:5:3'-triiodothyronine.<sup>28-31</sup> Characterization of this compound was possible by synthesis and separation from other iodinated substances by appropriate chromatographic solvent systems.<sup>5</sup>

Identification of the substances in the thyroid that are still unknown will require fulfillment of two preliminary conditions: first, the same compound must be prepared synthetically so

\* The following abbreviations have been used for different iodinated compounds and chromatographic solvent systems referred to in the figures: Tx = thyroxine; TRITH = triiodothyronine; DITH = diiodothyronine; MIT = monoiodotyrosine; DIT = diiodotyrosine; TRITA = 3:5:3'-triiodothyroacetic acid; I<sup>-</sup> = inorganic iodide; BuOH = n-butanol; Diox = dioxane; MeOH = methanol.

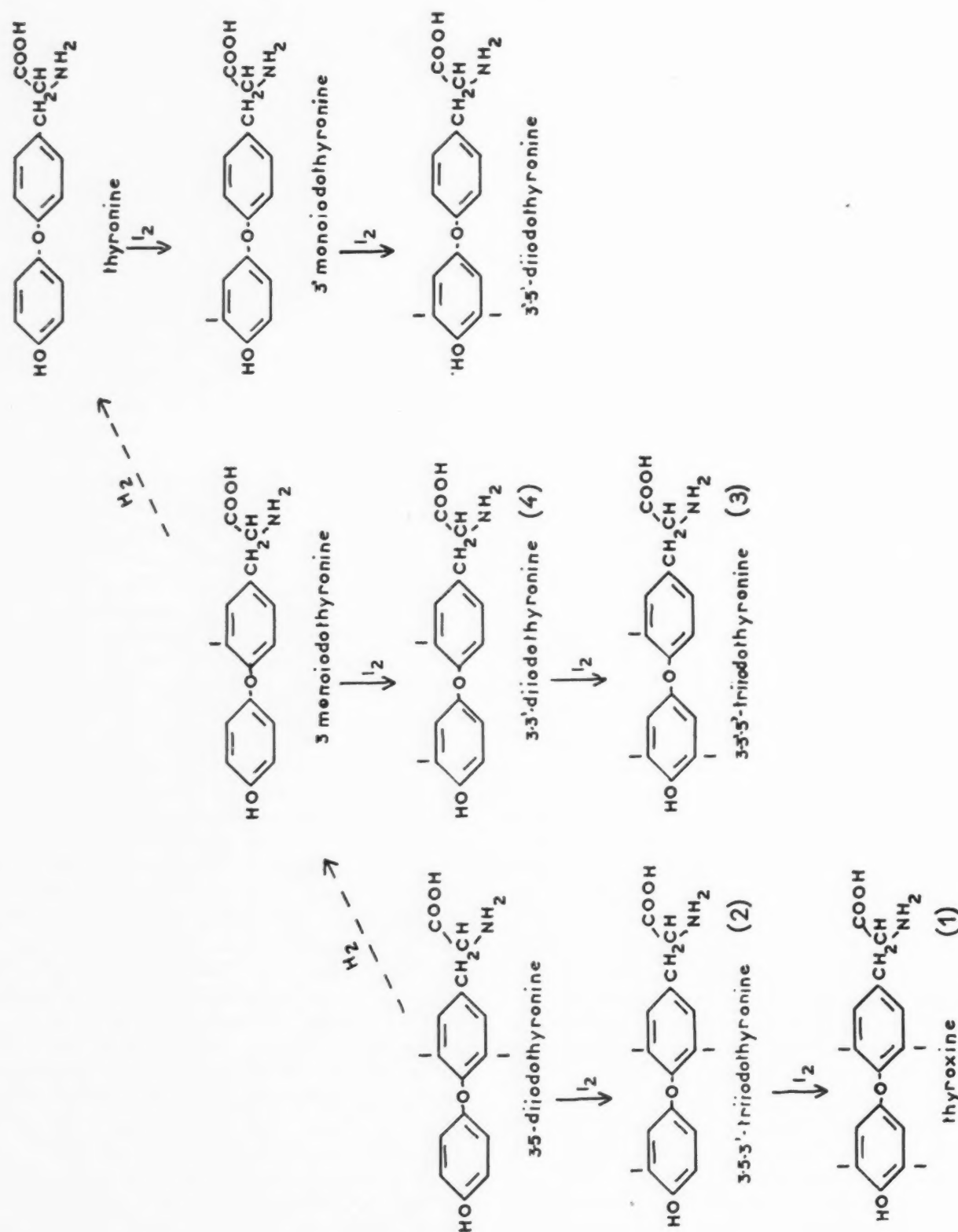


Fig. 3A. Reactions of halogenation and dehalogenation of thyronine and its derivatives.

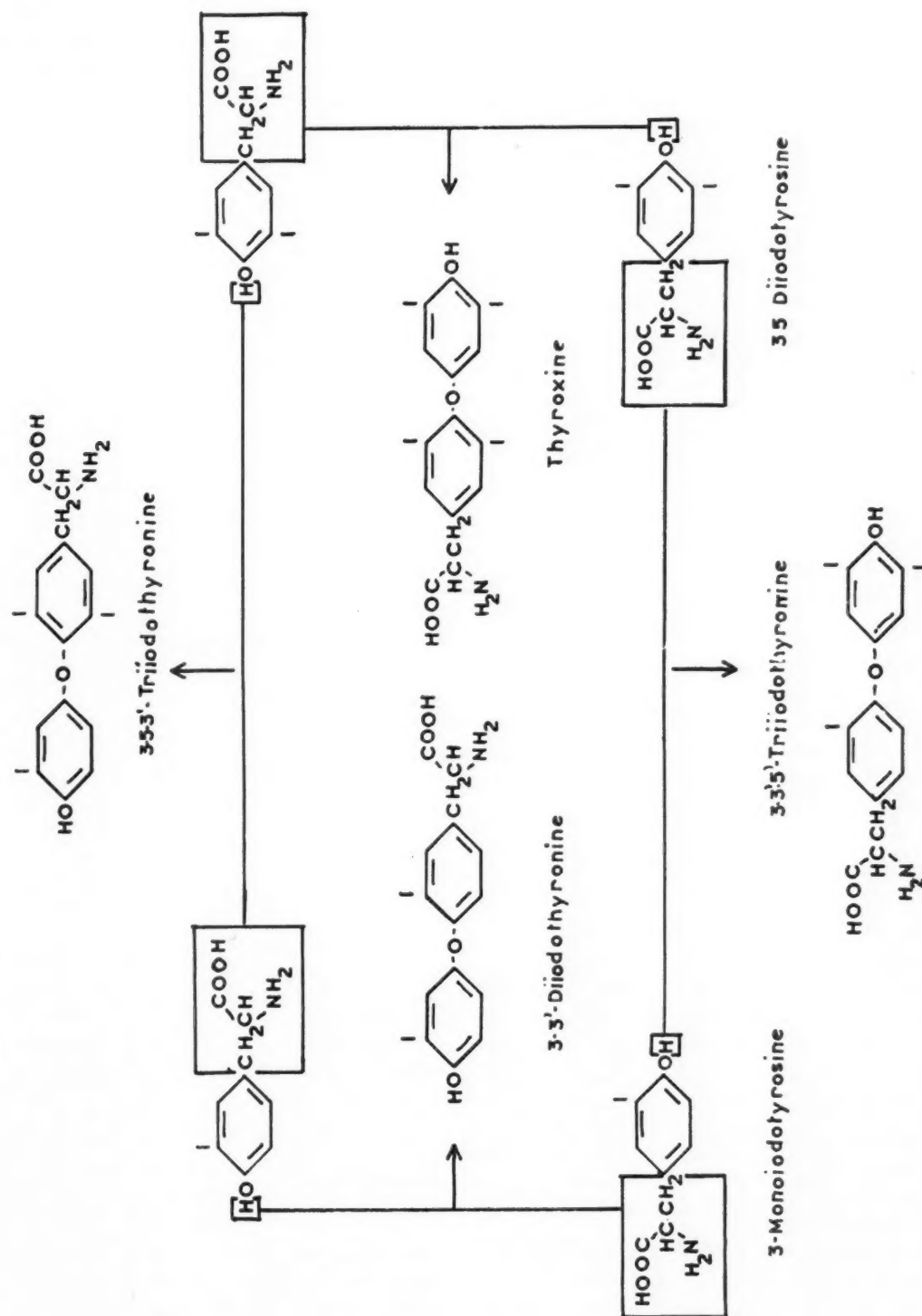


FIG. 3B. Possible reactions for the biosynthesis of iodothyronines.

B



that it can be used as a reference substance; then, it is necessary to develop chromatographic solvent systems to separate all the natural products identified from the new substances, which must then be separated from one another. If these conditions are fulfilled, and if the natural substance has exactly the same chromatographic properties as the reference material, their identity can be considered a possibility. To be certain of identity it will be necessary to make additional chemical studies.

The synthesis of 3:3'-diiodothyronine and 3:3':5'-triiodothyronine<sup>32</sup> and the development of convenient chromatographic solvents have made possible their identification as normal constituents of thyroglobulin.<sup>33,34</sup> (Fig. 2.) In the identification tests of these two iodothyronines the isolated substances always showed the same distribution and  $R_F$  values as the synthetic controls in seven solvent systems used and in one- and two-dimensional chromatograms. Obtaining 3:3':5'-triiodothyronine by the iodination of 3:3'-diiodothyronine provides conclusive proof of structure.<sup>35</sup> The presence of these two new constituents had previously been missed because with most of the chromatographic solvents used before, the spots had been confused with those of other components; either with thyroxine or with iodide and thyroxine (in the case of 3:3':5'-triiodothyronine) or with thyroxine and 3:5:3'-triiodothyronine (in the case of 3:3'-diiodothyronine). Identification of these two new iodothyronines brings to four the number of iodinated derivatives of thyronine present in the thyroid.

**Mechanism of Hormonogenesis.** The biologic formation of these two new thyroid constituents and of 3:5:3'-triiodothyronine may be attributed to a mechanism analogous to that of thyroxine, or it may be that thyroxine alone is formed from two molecules of 3:5-diiodotyrosine, the other constituents being derived from it by dehalogenation.<sup>29</sup>

While N-acetyl-thyroxine can be isolated after prolonged incubation of a solution of N-acetyl-diiodotyrosine,<sup>36</sup> it was not possible to detect the presence of N-acetyl-triiodothyronine in a solution of N-acetyl-monoiodotyrosine and N-acetyl diiodotyrosine.<sup>37</sup> This has given rise to the hypothesis that 3:5:3'-triiodothyronine can be formed by deiodination of thyroxine.<sup>2</sup> Yet in spite of the numerous trials carried out, no system capable of deiodinating thyroxine or any other iodothyronine has been found so far in the

thyroid.<sup>30,38</sup> However, even if a specific deiodinating enzyme system is present in the thyroid cells, it is very unlikely that it should limit its action only to the iodine atom in the 5' position without affecting the one in the 3' position at the same time; since the two positions are equivalent, such an enzymic process ought to lead to 3:5-diiodothyronine. Under these conditions how can the formation of 3:3'-diiodo- and 3:3':5'-triiodothyronine be explained? Another possibility is that 3:5:3'-triiodothyronine is derived by the partial iodination of less iodinated substances, thyronine or 3:5-diiodothyronine. Now, thyronine does not appear to be a natural substance for it has never been identified either in thyroglobulin or in any other protein. Even if present, study of its *in vitro* iodination, which yields only 3'-monoiodothyronine and 3':5'-diiodothyronine and no other iodothyronine,<sup>32</sup> eliminates the possibility of synthesis of the two 3:5:3'- and 3:3':5'-triiodothyronines and also of 3:3'-diiodothyronine. The possibility that 3:5-diiodothyronine can be further iodinated, as can be accomplished *in vitro*, must await demonstration of biosynthesis of the parent compound itself and especially its presence as a constituent of the thyroid gland. The chemical precursor of 3:3'-diiodo- and 3:3':5'-triiodo thyronines could be 3-monoiodothyronine, a substance the existence of which is even more hypothetical.

Figure 3A shows that halogenation and dehalogenation do not follow identical chemical pathways.

The possibilities which follow upon extension to other iodothyronines of prevailing views of the formation of thyroxine deserve to be considered. The diagrams in Figure 3B show the different possible reaction processes. This hypothesis is the one which conforms best to experimental facts: that is to say, that four iodothyronines are present simultaneously and that labeled 3:3'-diiodothyronine and 3-monoiodotyrosine appear soon after administration of labeled iodide to an animal. The abundance of thyroxine and 3:3'-diiodothyronine as compared to the small quantities of the two triiodothyronines might be explained by the fact that condensation of asymmetric molecules, chemically possible, must be more difficult than that of symmetric molecules.<sup>2</sup> The intermediate steps of the condensation are even more hypothetical;<sup>21</sup> study of these reactions is complicated by the fact that hormonogenesis

does not appear to take place from free amino acids but in the midst of a protein, thyroglobulin.

BIOLOGIC MECHANISMS LEADING TO THE SECRETION  
OF IODINATED PRODUCTS OF THE THYROID;  
NATURE OF BLOOD IODINE

*Products of Thyroid Secretion.* Almost all of the thyroid iodine is contained in a protein molecule which possesses certain special characteristics.<sup>2</sup> The 3:5-diiodotyrosine and thyroxine in part occupy a free N-terminal position;<sup>40</sup> as is the case for alanine,<sup>41</sup> a very small fraction can be considered to derive from the loss of the alanine chain during biosynthesis of thyroxine by condensation of two molecules of 3:5-diiodotyrosine. Another characteristic of thyroglobulin is that it is a glycoprotein,<sup>42,43</sup> of molecular weight, estimated to be 680,000. It is because of the large size of this molecule that thyroglobulin is held in the colloid vesicles<sup>10</sup> except in certain cases, as for example when the cell membrane is destroyed by irradiation.<sup>44,45</sup> The essential role of thyroglobulin is to serve as a store of hormones which, when freed by enzymic proteolysis,<sup>46,47</sup> become diffusible. The protease system, a cathepsin, has been isolated and purified and its study undertaken.<sup>48</sup> It has certain enzymic similarities with pepsin<sup>49</sup> but its essential biologic characteristic is that it does not preferentially release the iodothyronines from thyroglobulin.<sup>47,50</sup> Besides, the small fraction of iodinated compounds found in the thyroid gland, which includes 3-monoiodotyrosine and 3:5-diiodotyrosine as well as the iodothyronines, comes from proteolysis due to cathepsin.<sup>18</sup> A sort of physiologic selection comes into play from then on, due to an enzyme system specifically deiodinating the iodytyrosines<sup>38</sup> but devoid of any action on thyroxine, 3:5:3'-triiodothyronine, 3:3'-diiodothyronine and probably 3:3':5'-triiodothyronine. The thyroid dehalogenase has an optimum pH of 7; it is activated by thyroid-stimulating hormone and inhibited by an excess of thyroxine.<sup>56</sup> It has a direct effect on 3:5-diiodotyrosine from which it removes one atom of iodine, yielding 3-monoiodotyrosine which is deiodinated in turn to tyrosine.<sup>38</sup> Pyruvate and alpha ketoglutarate do not enhance the activity of the thyroid enzyme, in contrast to hepatic deiodinase.<sup>52</sup> Iodine liberated by dehalogenation of iodytyrosines is reincorporated into thyroglobulin; it can be assumed that almost all of the iodine entering the thyroid gland leaves it in the form of hor-

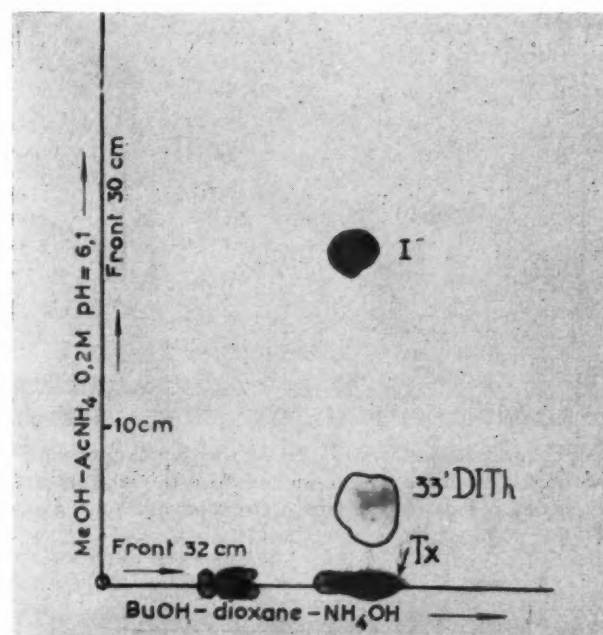


FIG. 4. Autoradiography of a two-dimensional chromatogram of an n-butanol extract of plasma of rats twenty-four hours after administration of I-131 (100  $\mu$ c. carrier-free NaI\*, three animals).

mones after one or more passage in thyroglobulin. It is understandable, therefore, that blood taken from the thyroid vein of animals given radioiodide contains virtually only thyroxine and 3:5:3'-triiodothyronine;<sup>53</sup> thyroxine in greater amount than 3:5:3'-triiodothyronine. It is practically devoid of any mono- and diiodotyrosine although thyroglobulin contains twice as much of these compounds as iodothyronines.<sup>20</sup> Reutilization of iodine, at first combined in biologically inactive form, leads to an economy of this element. The gland being the site of recovery of halogen obtained from deiodinated amino acids, it follows that the amount of 3-monoiodotyrosine in thyroglobulin always remains quite high, which can favor the biosynthesis of partially iodinated iodothyronines.<sup>34</sup>

*Nature of the Iodine in the Blood.* The iodinated compounds secreted into the blood pass into the general circulation and are taken to all the tissues. The nature of the iodine in the blood is not yet completely elucidated;<sup>54</sup> nevertheless, two points are clear: the red blood cells contain only inorganic iodide, organic compounds being found in the plasma. The membrane of erythrocytes is impermeable to iodothyronines<sup>55,56</sup> but allows iodide to pass through;<sup>57</sup> in fact, a biologic and clinical test for thyroid function based on this differential property has been put forward.<sup>58,59</sup> Plasma iodine, as shown in Figure 4,

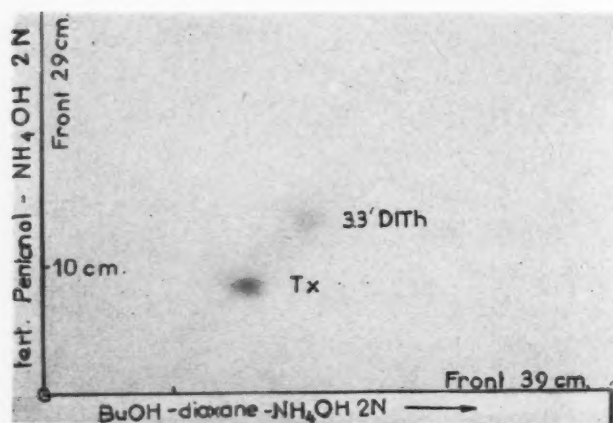


FIG. 5. Autoradiography of a two-dimensional chromatogram of a fractionated product of an n-butanol extract of plasma of rats twenty-four hours after administration of I-131 (100  $\mu$ c. carrier-free NaI<sup>\*</sup>).

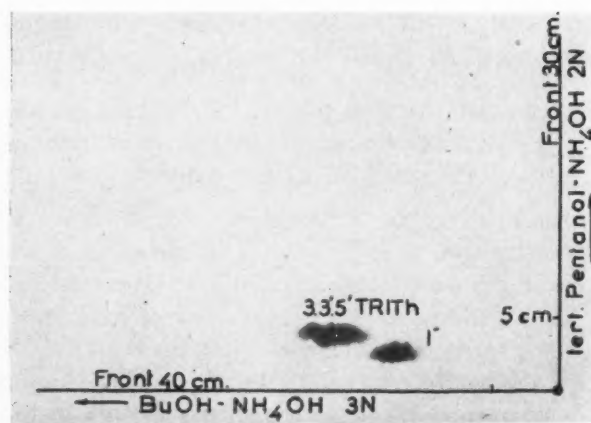


FIG. 6. Autoradiography of a two-dimensional chromatogram of a fractionated product of an n-butanol extract of plasma of rats twenty-four hours after administration of I-131 (100  $\mu$ c. carrier-free NaI<sup>\*</sup>).

is of a more complex nature; it is composed of 10 to 20 per cent inorganic iodide and 70 per cent thyroxine, the remainder being made up of different iodinated substances one of which is 3:5:3'-triiodothyronine.<sup>28,29</sup> This substance sometimes has not been found;<sup>60-62</sup> its presence depends upon the functional status of the thyroid gland.<sup>63</sup> Thyroglobulin has been shown to occur in the plasma in certain pathologic cases.<sup>64,65</sup>

Chromatographic analysis of plasma of rats given radioiodide has recently led to the characterization of two new constituents. One in which the chromatographic position in the usual solvents coincides with that of thyroxine, has been resolved by two-dimensional chromatography, and identified by referring to a synthetic substance. In seven different solvent systems the unknown substance has the  $R_f$  of 3:3'-diiodothyronine; hence this can be considered to be a normal plasma constituent.<sup>66</sup> (Fig. 5.) It appears very early in the blood and its concentration seems to decline later. In exceptional instances 3:3'-diiodothyronine may be present in quantities one-fourth of the amount of thyroxine. 3:3':5'-Triiodothyronine also has been identified in the blood of rats but is found in a very low concentration, so that its demonstration requires preliminary purification and enrichment of plasma extracts.<sup>67</sup> (Fig. 6.)

Other iodinated substances circulate in blood in very minute amounts; they do not appear to be iodotyrosines, as was once believed,<sup>63</sup> since chromatographic analysis with certain solvent systems excludes this possibility.<sup>66</sup> It is more likely that they are tissue metabolites of thy-

roid hormones but their nature has not been established.

Thyroxine and 3:5:3'-triiodothyronine are bound to some plasma proteins.<sup>68-71</sup> The type of attachment is not well known except that the binding is preferential for certain globulins, glycoprotein in nature.<sup>72</sup> Thyroxine is bound to plasma proteins more firmly than 3:5:3'-triiodothyronine.<sup>71</sup> The biologic importance of this fact is evident. Penetration of thyroxine into the cells is slower; it is in some way slowed down by its binding to proteins and its intracellular passage must be constantly regulated by a shift in the equilibrium from the plasma thyroxine complex toward fixation to cell proteins. The more labile binding of 3:5:3'-triiodothyronine favors its diffusion into tissues and partly explains some metabolic differences observed between the two hormones.<sup>73</sup> The origin of thyroxine in plasma is exclusively from the thyroid gland and probably this applies for the other iodothyronines as well, but it should be pointed out that in various pathologic cases 3:5:3'-triiodothyronine can arise, in part, from dehalogenation of thyroxine in the tissues.

#### METABOLISM AND BIOLOGIC ACTIVITIES OF THYROID HORMONES AND OF SOME OF THEIR STRUCTURAL ANALOGS

*General Metabolism of Thyroid Hormones.* The injection of physiologic doses of any of the iodothyronines is followed by excretion of the major amount of iodine in the urine and a much smaller fraction in the feces;<sup>56</sup> but the differences in the levels of elimination depend on the nature



of the substance administered.<sup>74</sup> Study of the fate of these compounds requires preparations of high specific radioactivity. 3:3'-Diiodothyronine is the most rapidly metabolized of all the iodothyronines since by the twenty-fourth hour almost 30 per cent of injected iodine is excreted by the kidney (less than 10 per cent of injected iodine is excreted in the case of thyroxine).<sup>75</sup> 3:5:3'-Triiodothyronine is utilized more intensely and rapidly than its isomer, 3:3':5'-triiodothyronine, which shows many similarities with thyroxine as regards the kinetics of urinary elimination. In the case of thyroxine and 3:5:3'-triiodothyronine, the speed of urinary excretion of the two radioisomers, one labeled in the ring bearing the alanine chain, the other in the phenolic ring, is different. The radioisomer labeled in the 3:5 position is more slowly degraded than the one labeled in the 3':5' position.<sup>76,77</sup> With these four iodinated derivatives<sup>78</sup> fecal excretion is less than urinary elimination.

Injection of four iodothyronines into animals is followed by temporary localization in the different regions of the digestive tract, especially the liver, but the rate of biliary excretion varies according to the substance administered,<sup>79-81</sup> as shown in Figure 7: thyroxine and 3:3':5'-triiodothyronine more slowly than 3:5:3'-triiodothyronine. As for 3:3'-diiodothyronine, the period of transit through the liver is very short, for in ten hours about 70 per cent of a physiologic dose goes through.<sup>82</sup> This passage is followed by enterohepatic circulation, the non-resorbed fraction in the intestine being excreted in the feces. A similar enterohepatic circulation has been shown for the other hormones, but it has been particularly well studied for thyroxine.<sup>79,81</sup> The fraction of hormones returning to the general circulation is distributed throughout the organism. 3:3'-Diiodothyronine is very rapidly extracted from the plasma to be distributed in the tissues in a non-specific manner.<sup>82</sup> This diffusion in the tissues is at a lower rate for 3:5:3'-triiodothyronine<sup>76</sup> and is still lower for the other two hormones. It should also be pointed out that the neurohypophysis of certain animals is capable of concentrating thyroxine and 3:5:3'-triiodothyronine<sup>73,83</sup> but it is as yet impossible to say if in the form of the hormones themselves or of one of their metabolites.

The injection of radiothyroxine is followed by the appearance in several tissues of radioactive iodinated substances one of which is inorganic

iodide.<sup>84</sup> The excretion of iodide in urine and bile that ensues indicates that peripheral dehalogenation of thyroxine is taking place, but the nature of the intermediate compounds formed is still not clear. 3:5:3'-Triiodothyronine has been demonstrated in the skeletal muscles of rats maintained on propylthiouracil for a long time and given thyroxine.<sup>85</sup> The specific dehalogenation of thyroxine can be thought of only as due to the action of an enzyme system. It is quite possible that the antithyroid agent affects this system and thus makes it possible to demonstrate the presence of 3:5:3'-triiodothyronine; similar experiments carried out with normal animals have failed to yield this compound.<sup>87</sup> 3:5:3'-Triiodothyronine is equally susceptible to peripheral dehalogenation but it is not possible at present to demonstrate the intermediate steps.

The hepatic and renal metabolism of intermediary thyroid hormones has been studied more fully and the results obtained are more significant than those in muscle.

*Hepatic and Renal Metabolism.* The liver rapidly concentrates all the thyroid hormones. The penetration of thyroxine into liver cells takes place in both nuclear and cytoplasmic structures; binding by mitochondria is not very intense.<sup>88,89</sup> *In vitro* studies have shown that thyroxine and 3:5:3'-triiodothyronine are rapidly concentrated by the mitochondria before reaching an equilibrium.<sup>90</sup> 3:5:3'-Triiodothyronine is accumulated more rapidly and in greater quantity than thyroxine; this phenomenon can be explained in part by the difference in binding force between plasma proteins and the two hormones.<sup>90</sup> The intracellular accumulation of thyroid hormones seems to be related to an increase in synthesis of coenzyme A.<sup>91-93</sup>

The substances formed in the liver and eliminated by the bile after administration of radioactive thyroid hormones have been identified by chromatographic analysis. Besides iodide and unchanged hormone, several radioactive spots of iodinated compounds appear on the chromatograms.<sup>81,94</sup> One of these is a product of glucuronic acid conjugation on the phenolic hydroxyl,<sup>95</sup> the amount of this derivative depending upon the nature of the iodothyronine given. The level is higher with thyroxine and 3:3':5'-triiodothyronine; it is lower with the other triiodinated isomer,<sup>94</sup> and still lower with 3:3'-diiodothyronine.<sup>76</sup> The amount of glucuronic acid conjugates formed in the liver is

I-131 %

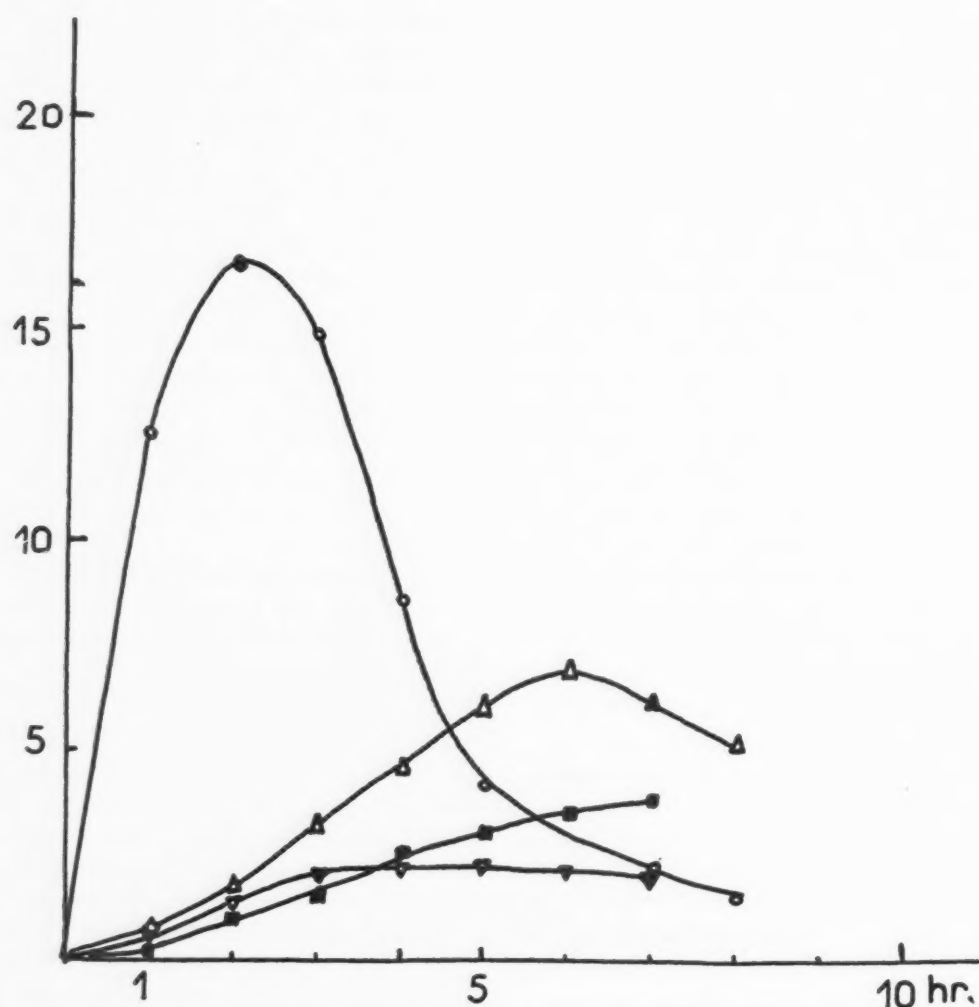


FIG. 7. Kinetics of biliary elimination per hour of the 4 labeled iodothyronines expressed in per cent of total radioactivity injected. Ordinate: per cent I-131 recovered in bile. Abscissa: time in hours after injection. —■—: thyroxine; —Δ—: 3:5:3'-triiodothyronine; —▽—: 3:3':5'-triiodothyronine; —○—: 3:3'-diiodothyronine.

inversely proportional to the speed of diffusion of the thyroid hormones in this organ.<sup>78</sup> The mechanism of glucuronic acid conjugation serves as a process of "detoxification" and as a means of regulation of the level of hormonal iodine.<sup>96</sup>

Another chromatographic spot has been identified in the bile of rats given labeled 3:5:3'-triiodothyronine. It is that of a keto-acid produced by oxidative deamination of this compound, namely, 3:5:3'-triiodothyropyruvic acid.<sup>80</sup> Its characterization has been established by a series of chemical reactions; those specific for alpha keto-acids and Pauly's reaction for a phenolic group are positive, the ninhydrin test gives negative results indicating the absence of a

free amino acid group.<sup>97</sup> A similar derivative is most probably formed from L-thyroxine, but at a lower rate. In the case of the D-isomer, which does not exist in nature, bile excretion and hepatic degradation are much slower;<sup>98</sup> the oxidative degradation of 3:3'-diiodothyronine is of limited extent.<sup>75</sup> An enzyme system which oxidizes 3:5-diiodotyrosine has been shown to be present in the liver.<sup>52</sup> It acts in the presence of ketoglutarate or pyruvate; however, it is not clear whether or not this system is responsible for the formation of the alpha keto-acids derived from iodothyronines.

The possibility of hepatic deiodination of thyroxine to triiodothyronine has been considered; the reverse reaction of iodination of the

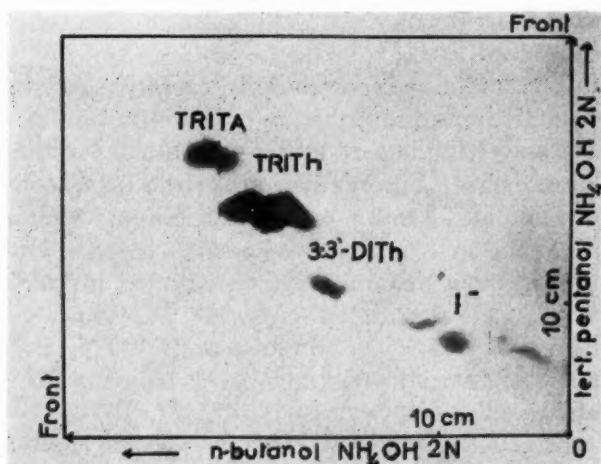
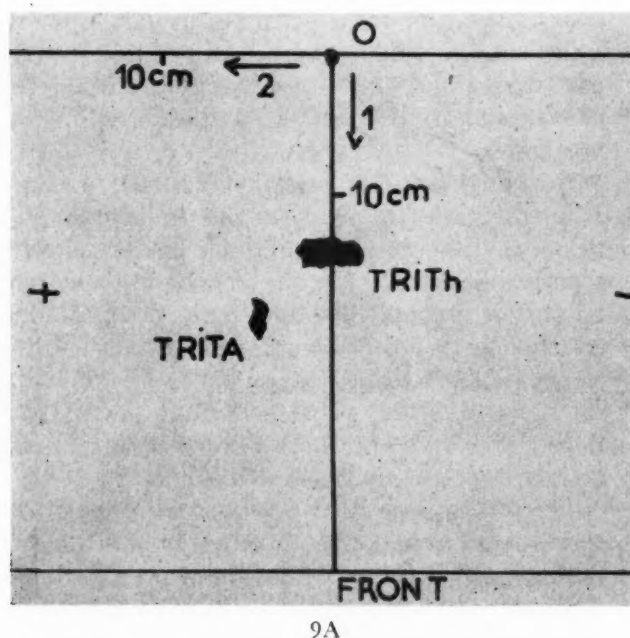
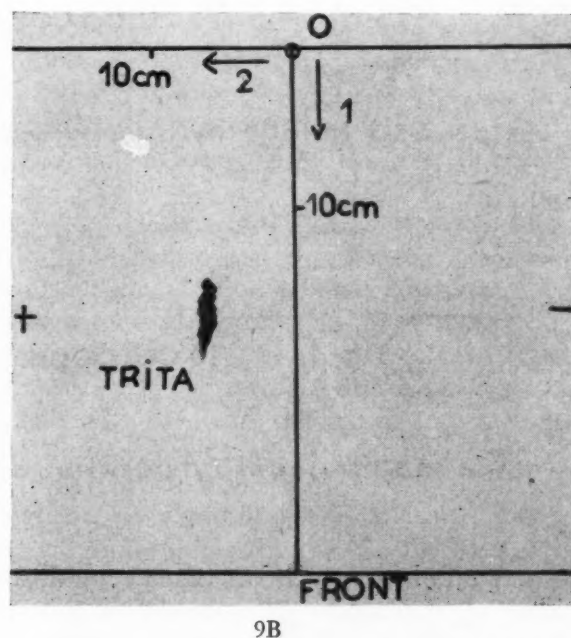


FIG. 8. Autoradiography of a two-dimensional chromatogram of rat kidney extract of animals given 0.25  $\mu$ g. of 3:5:3'-triiodothyronine labeled with I-131 in the 3' position.

indicating that the liver is not the only organ in which glucuronic acid conjugation occurs. The same seems to apply even for muscle. Injection of physiologic amounts of 3:5:3'-triiodothyronine, labeled in the 3' position, to the rat is followed within four hours by the renal concentration of 2 per cent of the total I-131 injected. Chromatographic analysis of the iodinated constituents of the kidney, as seen in Figure 8, shows the presence of four major iodinated compounds accounting for 96 per cent of the renal extract radioactivity.<sup>99</sup> Unchanged hormone constitutes the largest proportion of these substances; a small amount of inorganic iodide and 3:3'-diiodothyronine is also found.<sup>100</sup> The presence of 3:3'-diiodothyronine leads to the thought that dehalogenation has taken place in the kidney; as its catabolism is very rapid it is



9A



9B

FIG. 9. Autoradiography of a chromatoelectropherogram of rat kidney extract of animals given 0.25  $\mu$ g. of 3:5:3'-triiodothyronine labeled with I-131 in 3'. A, following fractionation by eluting a chromatogram zone corresponding to TRITH. B, following fractionation by eluting a chromatogram zone corresponding to TRITA. Dimension 1: chromatography with tertiary pentanol saturated with 2N  $\text{NH}_4\text{OH}$ . Dimension 2: electrophoresis 0.05 M  $(\text{NH}_4)_2\text{CO}_3$  buffer at pH 9.

latter has also been postulated but no formal indication of the proof of a specific dehalogenase has been obtained so far.

The renal metabolism of thyroid hormones has only recently been studied, both *in vivo* and with surviving kidney slices. The administration of thyroxine and 3:5:3'-triiodothyronine to eviscerated rats is followed by accumulation of these compounds in the kidney, together with inorganic iodide and glucuronic acid derivatives,<sup>87</sup>

unlikely that it is derived from other tissues.<sup>100</sup> A spot corresponding to 3:5:3'-triiodothyroacetic acid has been identified in aqueous extracts of the kidney and its presence has been confirmed by chromatography and electrophoresis, after purification.<sup>99</sup> 3:5:3'-Triiodothyroacetic acid either is formed in the kidney or is concentrated there. (Fig. 9.) Most likely it derives from oxidative decarboxylation of 3:5:3'-triiodothyroacetic acid, a product of



oxidative deamination of 3:5:3'-triiodothyronine, the presence of which in bile has been established. Figure 10 shows the structural formulas of these three compounds.

The existence of a renal dehalogenase that acts on thyroxine has been pointed out; surviving

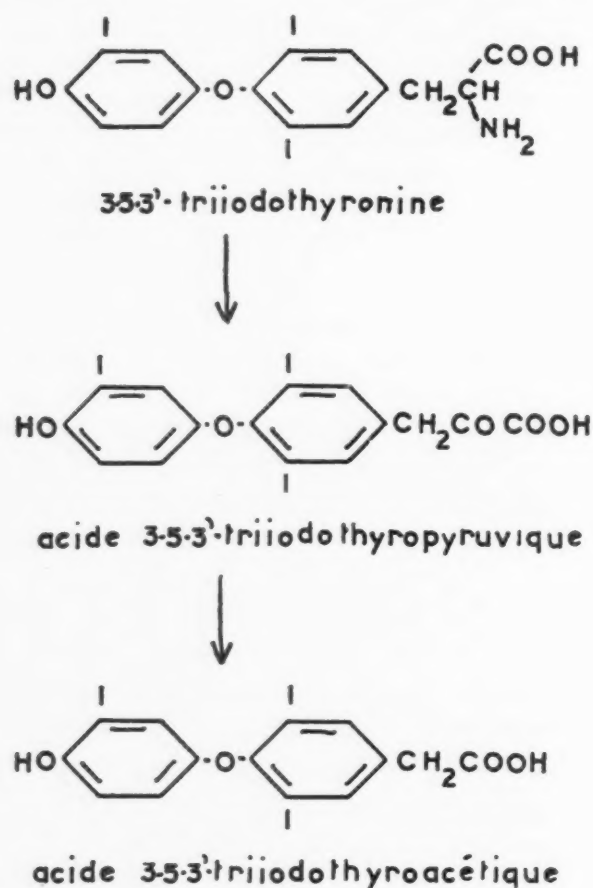


FIG. 10.

kidney slices to which are added very small doses of thyroxine are capable of partially deiodinating it to triiodothyronine;<sup>101</sup> after twelve hours of incubation dehalogenation occurs to the extent of 30 per cent with the kidneys of normal rats, 50 per cent with the kidneys of hyperthyroid rats but is less than 5 per cent in the case of thyroidectomized animals. The dehalogenating activity is suppressed by heating and is diminished by thiouracil and 3:5:3'-triiodothyronine. It appears that the activity of this enzyme system is very largely dependent upon the concentration of thyroxine in the tissue, but it is difficult to explain why, when the concentration is lowest, the enzyme is practically inactive. One wonders whether the presence of 3:3'-diiodothyronine in the kidney of rats given 3:5:3'-triiodothyronine is not due

to the action of renal deiodinase on the latter compound.

The iodinated compounds excreted by the kidney after administration of thyroid hormones are as yet inadequately defined. Besides a very large excess of inorganic iodide, the urine contains small amounts of organic iodinated compounds; one of these is probably tetraiodothyroacetic acid or 3:5:3'-triiodothyroacetic acid, according to whether or not tetra- or triiodothyronine is administered.<sup>102</sup> The corresponding acetic acid derivatives have not been identified so far.

Thyroid hormones, then, are metabolized in three principal ways: They undergo reactions of dehalogenation, since iodide is excreted by the kidney after their administration; detoxification processes lead to glucuronic acid conjugation; and finally, deamination followed by oxidative decarboxylation may occur. This last process transforms iodothyroacetic acids to thyroacetic acid derivatives, the biologic activities of which are known to be similar to those of thyroid hormones.

*Biologic Activities of Iodothyronines and of Certain Structural Analogs.* Study of the biologic activities of thyroid secretion products has raised two separate problems. On the one hand, research has been directed toward a comparison of the effectiveness of different hormones, using different biologic tests; and on the other, toward the nature of the substances that act at the tissue level and which are related to the intracellular metabolism of these hormones.

For a long time thyroxine was believed to be the only thyroid hormone since it had all the biologic properties of whole gland preparations. During recent years, after the isolation of 3:5:3'-triiodothyronine which is five to ten times as active as thyroxine (depending upon the test used<sup>1,29,103,104</sup>), it has been asked whether triiodothyronine is not the active form of thyroxine which would then serve merely as a reserve of hormone.<sup>29,105</sup> This view presupposes that the specific dehalogenation of thyroxine to 3:5:3'-triiodothyronine is accomplished with very high yield, for the formation of other iodothyronines would mean elaborating products that are less active than thyroxine itself. The other two naturally occurring iodothyronines possess activities of very different degrees.<sup>106,107</sup> 3:3'-Diiodothyronine has an antigoutogenic action of approximately the same degree as thyroxine (80 per cent of thyroxine) and has about the

same potency as thyroxine in tadpole metamorphosis. 3:3':5'-Triiodothyronine, in respect to these two tests, has only  $\frac{1}{20}$  of the activity of thyroxine or  $\frac{1}{100}$  of that of its isomer. At the present moment no explanation for this difference in behavior is at hand.

The varying biologic activity of the metabolites helps in studying the intracellular action of thyroid hormones. 3:5:3'-Triiodothyropyruvic acid is as effective as thyroxine in accelerating the metamorphosis of tadpoles while the tetraiodinated derivative has about one-third of this activity. Iodothyroacetic acids have, on the whole, the same properties as the thyroid hormones, but at times to a lesser degree.<sup>108-110</sup> 3:5:3'-Triiodothyroacetic acid has an anti-goitrogenic effect similar to that of D,L-thyroxine and increases the basal metabolism of rats within five days. But recent studies have shown that its action on the basal metabolic rate takes place very early: the administration of 10  $\mu\text{g.}/\text{kg.}$  of body weight of thyroidectomized rats raises the oxygen consumption by 60 per cent at the end of one hour, this effect being lost in about two hours.<sup>111</sup> It must be pointed out, however, that administration of this compound to patients with myxedema does not lead to any rise in their basal metabolism.<sup>110</sup> *In vitro* studies have shown that addition of iodothyroacetic acids to surviving kidney slices of thyroidectomized rats elicits an immediate rise in  $\text{QO}_2$  which has led some investigators<sup>112-114</sup> to believe that these compounds represent the active form of the hormones. Additional research on this problem is necessary before valid conclusions are possible.

The number of structural analogs of thyronine that have been synthesized and biologically tested exceeds 100. Studies of their biologic activity have been carried out to determine whether the intact molecule is necessary for hormonal activity or whether only certain structural elements are indispensable. Several general articles have been devoted to this question.<sup>20,105,115-117</sup> Some essential ideas can be drawn from them. Iodine can be replaced by other halogens.<sup>118,119</sup> Bromine and iodine are to some extent equivalent, 3:5-diiodo-3'-bromothyronine being about twice as active as thyroxine in respect to anti-goitrogenic action while 3:5-diiodo-3':5'-dibromothyronine is active only to a lesser degree.<sup>118</sup> The role played by the alanine side-chain in the iodothyronines is illustrated by the fact that deamination to the corresponding pyruvic acid or substitution of

a propionic or acrylic acid side-chain leads to reduction in anti-goitrogenic activities.<sup>106</sup> On the other hand, the presence of an acrylic or propionic acid side-chain considerably increases activity in respect to acceleration of amphibian metamorphosis;<sup>107,120</sup> for example, 3:5:3'-triiodothyropropionic acid is 300 times more active than thyroxine.<sup>107</sup>

#### CONCLUDING REMARKS

The conditions of structure required for thyroid activity have been discussed. For a long time it was believed that the presence of halogen in the 3 and 5 positions was indispensable for activity and that activity was greatly enhanced when halogen was also present in the 3' and 5' positions. At present, the first condition can be considered not indispensable, a single substituent in 3 associated with another in 3' suffices; nevertheless, a third substituent in position 5 greatly increases the activity, and diminishes it if in the 5' position. In general, whatever the aliphatic side-chain on the nucleus, a 3:5:3' substitution in the rings ensures maximal activity.<sup>107,118</sup>

The biologic activities of the substances comprising the thyroid secretion depend upon the nature of their metabolites, some of which are as active as the parent secretion products, so that one may well ask if it is not at the level of the cell that the active forms of the hormones are elaborated. The multiplicity of substances possessing hormonal properties complicates research in this field and the indirect effects which occur only by way of the pituitary make such investigation even more difficult. The concept of cellular utilization of thyroid hormones and their transformation peripherally into an active form of the hormone opens the way for future work.

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# Physiologic Concepts in the Diagnosis and Treatment of Graves' Disease\*

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**I**N some respects it is surprising that the etiology of Graves' disease remains unknown. Nevertheless the abundant clinical observations and productive research in thyroid physiology have given sufficient understanding of this disease that the therapy of the hyperthyroidism has become one of the most satisfactory therapeutic endeavors in medicine.

Graves' disease is not the only clinical condition accompanied by thyrotoxicosis. There are three causes of hyperthyroidism. The etiology of two is well known but that of the third, Graves' disease, remains obscure. Thus the thyroid hormone may be taken by mouth in excessive quantities, producing thyrotoxicosis factitia; one or more adenomas of the thyroid may, without respect for bodily need, produce excessive quantities of thyroid hormone and thereby be the cause of thyrotoxicosis. When the source of the thyroid hormone is eliminated in each of these two instances, the problem is clearly and decisively solved.

## CLINICAL PATTERN OF THE DISEASE

Graves' disease (sometimes called Parry's disease or Basedow's disease) is a rather complex clinical entity with several facets. The classical clinical picture of Graves' disease consists of (1) the symptoms of hyperthyroidism, which apparently are attributable to an excess of thyroid hormone; (2) a variety of unique signs associated with the eyes, the most striking being exophthalmos; and (3) goiter which, when it is conspicuous, rounds out the picture of Graves' disease as it has been commonly seen. The original descriptions, especially those of Graves<sup>1</sup> and von Basedow<sup>2</sup> included these three features. In the minds of some, the diagnosis of Graves' disease is not permissible until all of these facets of the disease process have become evident.

Several terms have been used as synonyms for Graves' disease. "Exophthalmic goiter" may not be appropriate if the subject fails to show signs about the eyes or does not have goiter. "Diffuse toxic goiter with hyperthyroidism" distinguishes the disease from that produced by a hyperfunctioning adenoma, but if no enlargement of the thyroid is present the term is inappropriate. "Thyrotoxicosis" is not specific as to the source of excessive thyroid activity and, indeed, Graves' disease may occur without hyperthyroidism.

Because students of the disease now recognize that any one of the several facets of the disease may become evident before the others, the application of the diagnosis of Graves' disease has become broadened. As in any disease there must be a beginning. Not infrequently one of the triad of signs of Graves' disease will precede the others. It is for this reason that early diagnosis is sometimes difficult because all patterns of the disorder do not evolve simultaneously. If there is one aspect of Graves' disease that is most likely to precede others, it is the symptoms associated with hyperthyroidism. This is the basis for the early diagnosis of the disease, although severe degrees of hyperthyroidism may be found before there is any appreciable enlargement of the thyroid. If hyperthyroidism is observed first, it is usually corrected without delay. Subsequently another facet of the disease, exophthalmos, may appear.

Instances occur in which exophthalmos, a true forward displacement of the eye, may precede all the other symptoms and indeed may occur in only one eye. Weakness of some extraocular muscles or perhaps only an unexplained irritation about the eyes may appear. Without clinical or even laboratory evidence of thyrotoxicosis and without a goiter, these patients often come to the attention of the ophthalmolo-

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gist first and may receive a presumptive diagnosis of orbital tumor before other facets of the disease become evident. On rare occasions a slight lid retraction or "a certain look in the eye" is the heralding sign of ophthalmopathy and Graves' disease. Although the protein-bound iodine level of the serum and the radioiodine uptake test may fail to show evidence of increased thyroid activity, a diagnosis of Graves' disease should seriously be considered.

Some instances occur in which a diffuse enlargement of the thyroid gland is the only finding. This may, for quite a period of time, be regarded as a simple or colloid goiter before the other manifestations of the disease become evident.

Perhaps a less tangible facet of Graves' disease is emotional instability. Many authors have regarded psychic trauma as a precipitating cause of Graves' disease because such a history is often readily obtainable. On the other hand, a patient with only latent emotional instability may develop a major psychiatric problem as a result of Graves' disease. Thus it is debatable whether or not the peculiar emotional instability is the cause or the effect of the underlying disease. In any event, if these features of emotional instability are presented as the sole symptom, it is unlikely that the physician would make a diagnosis of Graves' disease. However, case histories of patients with Graves' disease repeatedly reveal stories of nervousness, irritability and personality clashes at a time when the best diagnostic skill could find no definite proof of the disease. Occasionally with some uncertainty a diagnosis of chronic nervous exhaustion, anxiety neurosis or neurocirculatory asthenia is made. The clinical features which lead to one of these diagnoses may have been the subtle beginning of Graves' disease in at least some of these patients. The odd pattern of emotional behavior is not solely attributable to excessive thyroid hormone, nor is the peculiar atmosphere of tenseness, jumpiness, anxiety, restlessness and the many useless yet purposeful movements attributable to excessive thyroid hormone, as will be shown later. These disturbances are probably related to the underlying causative factor of the whole disease.

#### DISTINCTION BETWEEN GRAVES' DISEASE AND TOXIC NODULAR GOITER

In 1913 Plummer<sup>4-6</sup> presented evidence to show that hyperthyroidism produced by hyper-

functioning adenomas was a clinical entity distinct and separate from that of Graves' disease.<sup>7</sup> Although some uncertainty as to the distinction between these two diseases has existed until recently, the differences in the pathologic anatomy and physiology have been fully confirmed by the use of radioactive iodine.<sup>8</sup> (Figs. 1 and 2.) In one, which shall be referred to as toxic nodular goiter, hyperthyroidism is due to one or more adenomas that produce excessive amounts of thyroid hormone irrespective of the needs of the body. In the other, Graves' disease, all the non-adenomatous thyroid tissue becomes overly active in response to some unknown stimulus as a part of a more generalized disease process.

These two diseases differ in several aspects. The approximate date of onset of Graves' disease, particularly in a young person, is usually fairly well defined, in contrast to the insidious onset of symptoms in toxic nodular goiter. Plummer<sup>6</sup> observed from a review of 2,000 patients whose conditions had been diagnosed as toxic nodular goiter that the average period between discovery of a mass in the thyroid and onset of symptoms of hyperthyroidism was seventeen and a half years. The average age of persons with Graves' disease is ten to fifteen years younger than patients suffering from toxic nodular goiter, although admittedly there is considerable overlap among the two groups.

Three clinical features stand out most clearly as key differences in the two diseases. These are general behavior, exophthalmos and response to iodine therapy. Patients with Graves' disease usually display significantly more emotional instability, restlessness, tension and useless but purposeful movements than do patients with toxic nodular goiter, who sit quietly and tell their stories with a minimum of movement or emotional display. It is customary for the physician to underestimate by half the basal metabolic rate of a patient who has toxic nodular goiter, if his judgment is based on experience with the high-strung vivacious nervousness of Graves' disease. Whereas the patient with Graves' disease will emphasize his nervousness and other features of a stimulated state, the patient with toxic nodular goiter is far more inclined to complain of cardiac symptoms.

Although exophthalmos is by no means always found in Graves' disease, it is very common. In contrast, exophthalmos is very rarely if ever found in patients with toxic nodular goiter.



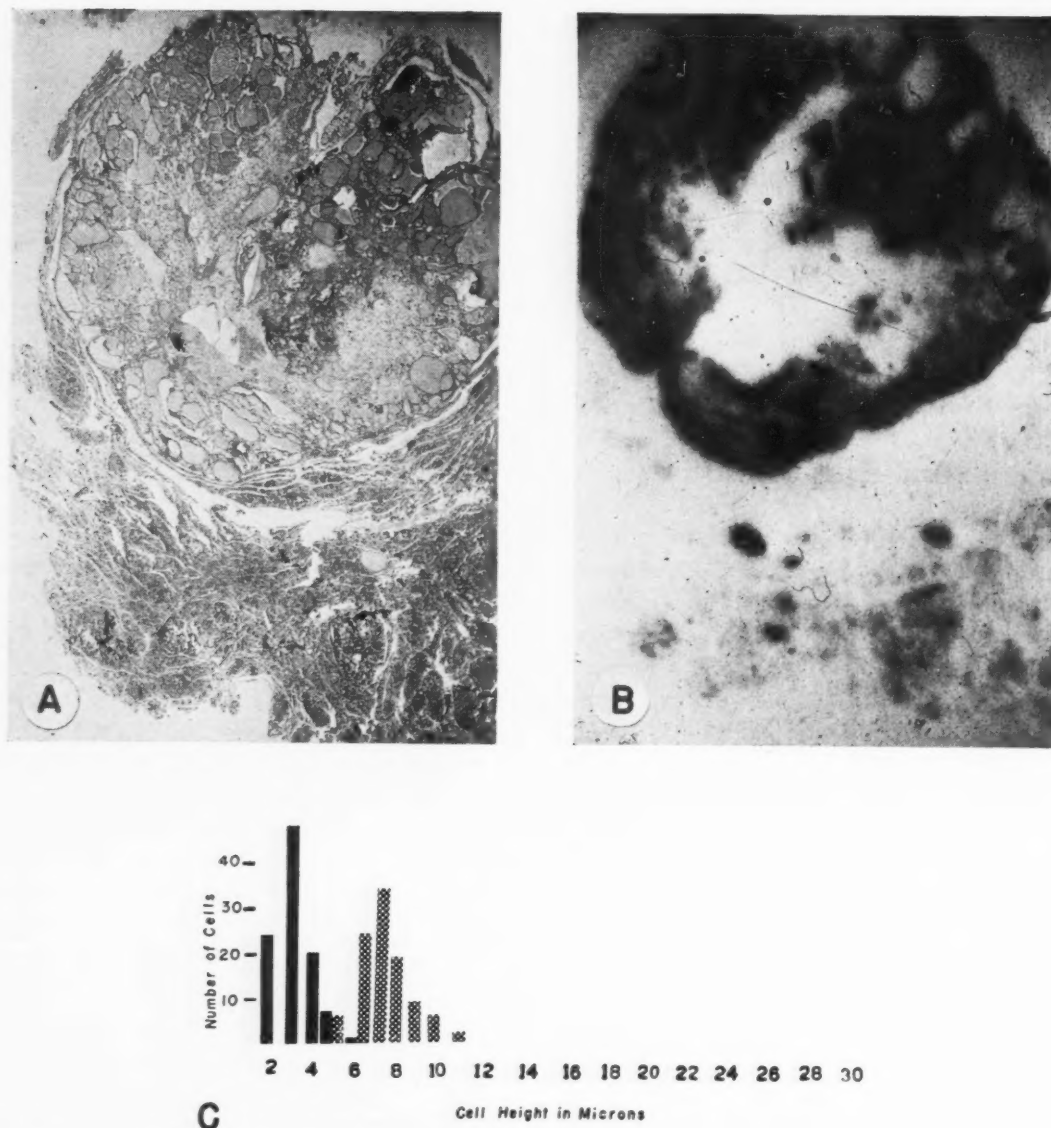


FIG. 1. Radioautographs illustrating the difference between (1) hyperfunctioning adenoma with thyrotoxicosis and (2) Graves' disease with an incidental adenoma of the thyroid. The microscopic sections (A) coincide with their radioautographs (B) in each figure. The dark areas on the radioautographs serve to identify the location of excessive thyroid function. The clinical pattern of disease produced by the autonomous adenoma in Figure 1 is different from that associated with diffuse overactivity of the whole gland in Figure 2. (C) in each figure illustrates the height of the cells in each type of tissue. (Based on 100 cells measured in each type of tissue.) The checked columns represent the cell height distribution in the adenoma while the solid columns represent that of the extranodular tissue. In Figure 1 the adenoma is composed of tall active cells while the cell height in the extranodular tissue is suppressed below the average of 5 microns usually seen in normal persons; in Figure 2 the extranodular tissue is composed of tall cells that are responding to some unknown stimulus that is a part of the broader disease pattern known as Graves' disease.

Rice<sup>9</sup> found ten patients with exophthalmos in a group of 121 whose condition was diagnosed clinically as toxic nodular goiter; the diagnosis was based presumably on the fact that the patients were thyrotoxic and had lumps in the thyroid glands. In each of the ten patients with exophthalmos, cellular hypertrophy and hyperplasia were found in the extranodular tissue, thereby showing that the diagnosis should have been Graves' disease and not toxic nodular

goiter. Over a period of ten years the author<sup>10</sup> has made radioautographs from several hundred nodular goiters, seeking particularly those patients with eye signs. No instance has been found in which true eye signs were present when excessive uptake of radioiodine was located in an encapsulated nodule. Paranodular tissue was found to be the site of excessive activity, indicating the correct diagnosis to be Graves' disease.

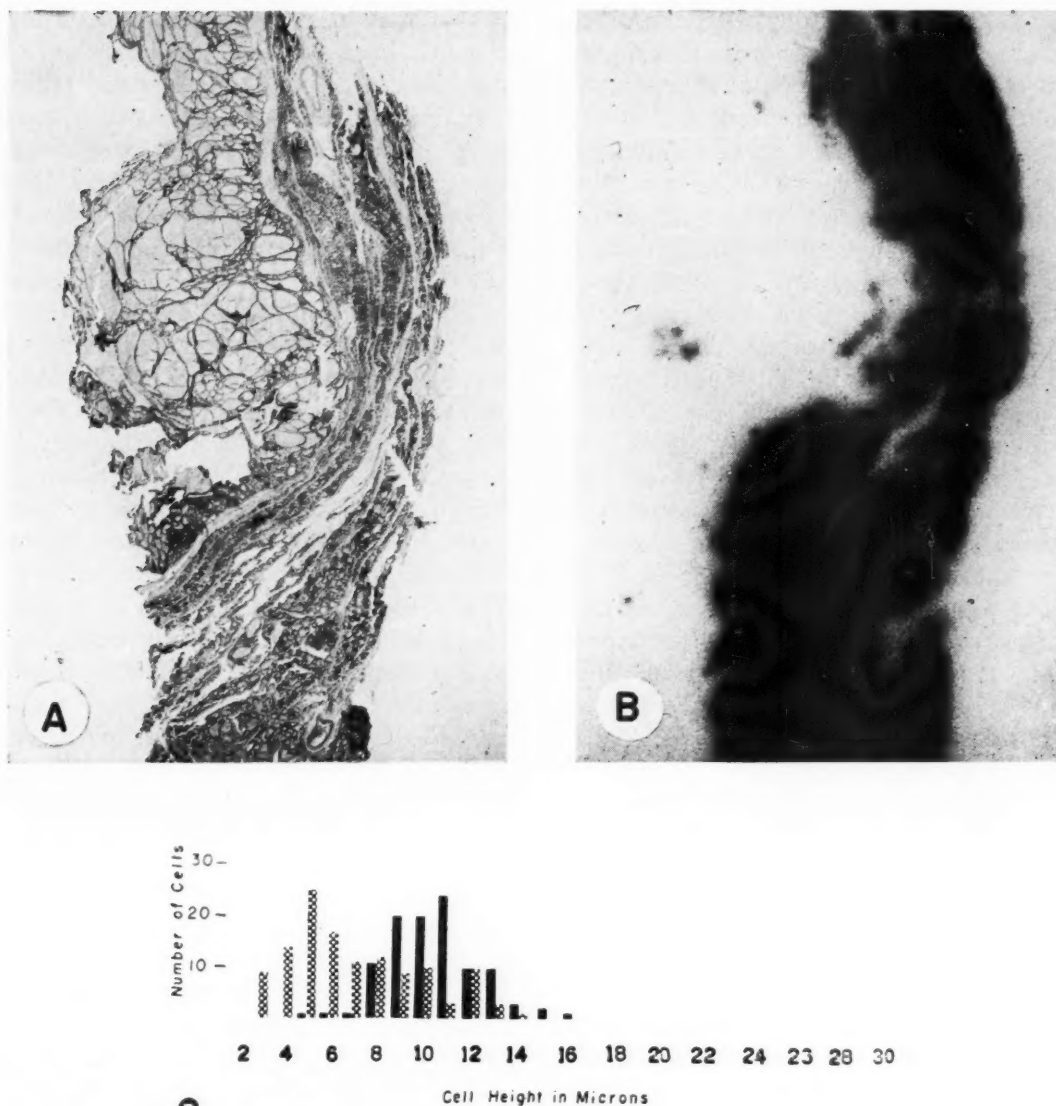


FIG. 2. See legend on opposite page.

When Plummer was firmly establishing the therapeutic value of iodine administration in Graves' disease in 1922, it became evident that there was a difference in the response to iodine administration in these two types of patients. Those with Graves' disease responded with dramatic improvement within a few days, while those with toxic nodular goiter were unaffected or occasionally toxicity increased. In the former a strange quieting effect resulted, the bruit in the gland diminished within hours, the myasthenia improved and the patient recognized the change promptly. A further distinction in the response to iodine in patients with Graves' disease was an increase in firmness of the gland. This effect was not achieved in patients with toxic nodular goiter. Trial administration of iodine became one

of the most convincing diagnostic maneuvers the physician could use. This differential diagnostic observation was of relatively less use to clinicians dealing with patients who lived where iodine was abundant, as in coastal areas. It is probably for this reason that some clinicians in iodine-abundant areas failed to accept this point of difference between toxic nodular goiter and Graves' disease.

Plummer,<sup>7</sup> in a statistical study based on approximately 15,000 patients in whom bilateral subtotal thyroidectomy had been performed, found the recurrence rate in Graves' disease to be 6.5 per cent. In contrast, among 2,000 patients in whom the condition had been classified as nodular goiter with hyperthyroidism (the pathologic examination showing no diffuse

extra-adenomatous hypertrophy) the recurrence of hyperthyroidism was 0.1 per cent. This highly significant difference in recurrence rates served further to distinguish the two diseases.

It goes without saying that physical examination of the thyroid assists the clinician in obtaining a differential diagnosis between toxic nodular goiter and Graves' disease. It is not as simple as determining the presence or absence of nodules, however, because such masses might be only a coincidental feature and might have nothing to do with hyperthyroidism, thus confusing the physician who is palpating the thyroid. Graves' disease may develop in a patient who already has a nodular goiter. Rice<sup>9</sup> showed that the incidence of nodules in patients with Graves' disease was exactly the same as the incidence of nodules in normal persons of similar age. If by chance only one or two hyperfunctioning nodules are present and the patient has hyperthyroidism, atrophy of the extranodular tissue (recognized by Wilson,<sup>11</sup> Boothby,<sup>7</sup> Rice,<sup>12</sup> Hendrick<sup>13</sup> and Cope et al.<sup>14</sup>) makes all tissue other than the nodule non-palpable.

Thus Plummer<sup>6,9,22</sup> was able to define on purely clinical grounds, with an accuracy of approximately 95 per cent, three clinical entities: the diffuse hyperplastic gland of Graves' disease, the nodular goiter containing incidental tumors coincident with Graves' disease, and the toxic nodular goiter with hyperfunctioning nodules.

#### THYROID-STIMULATING HORMONE (TSH) AND GRAVES' DISEASE

It has been postulated by some that Graves' disease is caused by excessive production of thyroid-stimulating hormone from the anterior pituitary. This deduction was an outgrowth of the demonstration that exophthalmos, goiter and signs of hyperthyroidism appeared promptly in animals given pituitary extracts. The similarity was further substantiated by certain changes in skeletal muscle, increased oxygen consumption and increased amounts of protein-bound iodine in the serum. Relatively little attention, however, was given to the fact that the condition could not be maintained by repeated injections and that the immediate response was only mildly or not at all affected by iodine administration. It now seems adequately proved that there is a normal interrelationship between the anterior pituitary and the thyroid, but the evidence that abnormal activity in the pituitary is the cause of Graves' disease seems considerably more tenuous.

The fact that the unique combination of exophthalmos and hyperthyroidism results from administration of anterior pituitary extract while only hyperthyroidism can be produced by known products from the thyroid constitutes one argument in favor of the pituitary as against the thyroid being the primary seat of the disorder. But, if the normal biologic response of the anterior pituitary to thyroid hormone production is in effect in Graves' disease, then the pituitary output of TSH\* should decline when the thyroid is excessively active. Assay data suggest that this is the case and thus support the belief that the pituitary is not to blame. Although methods for assaying TSH in the blood and urine have lacked the desired sensitivity until very recently, the large collective experience in the literature reveals repeated failures in detecting TSH in Graves' disease, but by those same methods it was repeatedly demonstrable in normal persons and found in increased amounts after destruction of the thyroid. Werner and his associates<sup>15</sup> have shown that the thyroid gland of patients with Graves' disease receiving iodine will release increased amounts of serum-precipitable iodine when only small amounts of exogenous TSH are given. It would seem unlikely then that a small amount of this material could have such an influence if the endogenous supply of TSH were excessive. Werner has also shown that the administration of triiodothyronine has relatively little effect in suppressing the I-131 thyroid uptake in Graves' disease, as it has in normal thyroid glands. Werner's work thus suggests that Graves' disease is not dependent upon pituitary activity.

It has been shown by Rawson and his associates<sup>16</sup> that hyperplastic thyroid tissue inactivates TSH *in vitro* more readily than does normal thyroid tissue. It has also been shown by Loeser<sup>17</sup> and Seidlin<sup>18</sup> that exogenous TSH disappears from the circulation of a normal animal more rapidly than from an animal in which the thyroid has been removed. Thus it may be argued that there may be excessive TSH production in Graves' disease but that it is inactivated so rapidly it is not detectable in the blood.

Although the production of TSH may not be increased in Graves' disease, it is conceivable that the thyroid might have an increased sensitivity to TSH, the sensitivity of the thyroid perhaps being dependent on another endocrine

\* Thyroid stimulating hormone.



gland. At this time evidence for such a mechanism is lacking.

Thus one of two situations must exist in the relationship between the thyroid gland and the anterior pituitary gland in Graves' disease: (1) The thyroid independently produces an excess of thyroid hormone and the pituitary responds with diminished output of TSH or (2) the pituitary produces excess TSH but it does not respond in the usual manner to the resulting excess of thyroid hormone; the TSH is not detectable because the thyroid inactivates it. The first postulate seems more plausible.

#### STRUCTURAL CHANGES IN THE THYROID

The histologic changes in the thyroid associated with Graves' disease are well known. With increased thyroid activity the follicular colloid which normally stains deeply becomes lighter and vacuolated near the periphery or becomes so markedly reduced in quantity that it appears frothy. An increase occurs in the height of the thyroid epithelium from about 5 microns in the normal subject to 10 to 15 microns in the subject with Graves' disease. The normally flat epithelium of the thyroid thus becomes cuboidal, and because there is proliferation as well as hypertrophy of cells they become not only columnar in appearance but, as if by crowding, produce raised papillary formations protruding into the follicle. The nucleus, which was formerly flat and deeply stained, increases in size and becomes spherical; the chromatin becomes finely granular or even vesicular. Droplets appear in the cytoplasm and may become so abundant that the cytoplasm of the cell becomes frothy and indistinctly delineated from the adjacent colloid. Observations made on animals in which the thyroid was made hyperactive by administration of thyrotropic hormone have served to illustrate how these droplets in the cytoplasm form and move along the lateral margin of the cell toward the basement membrane, presumably to be released into the circulation.

Although the size of the follicles may be diminished, the hypertrophy and particularly the proliferation of the cells usually lead to marked enlargement of the whole gland. The increase in vascularity of the gland also contributes markedly to its size. It should be kept in mind that the thyroid in some cases of Graves' disease is not found to be particularly enlarged. The epithelium nevertheless will show greater than

normal height. Presumably there is relatively less proliferation of cells in such a gland but the increased functional capacity is easily demonstrated.

#### INVOLUTIONAL EFFECT OF IODINE

Administration of iodine causes very prompt reduction in size and increased firmness of the gland. Much of the change is due to decreased vascularity. The height of the thyroid epithelium is markedly reduced and colloid is again stored in the follicles. This resolution toward normal is not uniform. Minute areas remain which bear histologic signs of intense activity. Occasional papillary projections into the follicles are still found.

This reaction, although well known for many years, remains unexplained. Excessive amounts of the administered iodine are stored in the gland, as would be expected in such a seriously depleted gland. However, it has been shown by Rawson et al.<sup>19</sup> that accumulation of iodine in the thyroid is not necessary for this involutional reaction to occur. Biopsy specimens were obtained of hyperplastic thyroid glands from patients with Graves' disease before any treatment was given. Thiouracil was then given in doses which effectively blocked the uptake of iodine by the gland. In addition, relatively large doses of iodine were given but essentially none was collected by the thyroid. Subsequent studies of biopsy specimens some days later revealed that the involuting effect had occurred. The cell heights had been reduced from 12 microns to 7 and a marked increase had been noted in the staining quality of the colloid. This important observation suggests that iodine, in producing the involutional effect, acts primarily on some structure other than the thyroid gland and that the change in the thyroid is perhaps secondary.

Graves' disease is an illness which shows cyclic variations,<sup>5,21</sup> as illustrated in Figure 3. The fluctuations in the disease, as measured by the basal metabolic rate, usually show swings with increasing severity as time passes. An appreciation of this pattern of the disease is important from the standpoint of management. If iodine administration is begun and appreciable improvement does not occur, it should be understood that the condition is probably on an upswing and the patient would be more toxic had the iodine not been given. Because iodine is sometimes thought to be useless, it is withdrawn; in this case the patient's condition soon rises to a higher

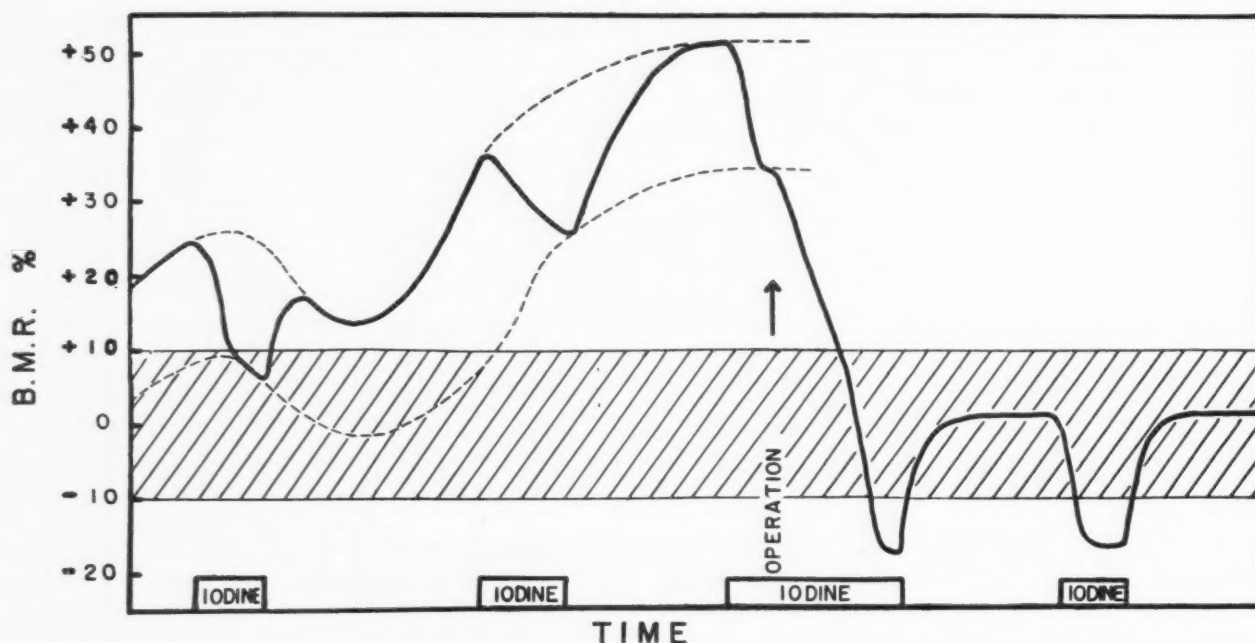


FIG. 3. Diagrammatic representation of the course of the hyperthyroidism of Graves' disease, after Means.<sup>21</sup> Graves' disease tends to show variation in intensity as the illness progresses,<sup>6</sup> shown by the upper wavy but gradually rising line. When iodine is given, the condition improves and under this influence progresses at a lower level, shown by the lower wavy line paralleling the upper one. If iodine is discontinued, the disease returns toward its former level. The response to iodine may appear more beneficial at some times and less beneficial at others, depending on the natural fluctuation of the disease. Following thyroidectomy the patient is in a euthyroid state after having lost a large portion of the thyroid gland. The administration of iodine continues to depress the metabolism (and may actually produce myxedema<sup>39,40</sup>), an action of iodine peculiar to Graves' disease.

plane and this is at times an initiating factor of thyroid storm.

#### LYMPHOCYTES AND GRAVES' DISEASE

The role played by lymphocytes in Graves' disease is probably far more important than can be appreciated at this time. One of the histologic characteristics sometimes regarded as diagnostic evidence of Graves' disease is the presence of lymphocytes scattered throughout the thyroid parenchyma.<sup>20</sup> In some instances germinal centers may be observed. Although some observers consider the presence of lymphocytes to be a morphologic requirement for diagnosis, it should be pointed out that in many patients who do not have Graves' disease occasional scattered lymphocytes have been noted in the thyroid gland. Furthermore, large numbers of lymphocytes may be found in the thyroid glands of some patients who show evidence of hypothyroidism. Thus the pathologist may find varying degrees of lymphocytic replacement in thyroid glands, a spectrum which might include struma lymphomatosa. In this connection it is interesting to point out that, at the time the surgical mortality rate in the treatment of Graves' disease was dangerously

high, some patients were able to withstand hyperthyroidism for a period of years and ultimately experienced complete remission.<sup>21</sup> Some of these patients actually became hypothyroid, and the glands were ultimately found to be extensively replaced by connective tissue and lymphocytes.

Kocher called attention to the relative lymphocytosis commonly found in the peripheral blood of patients with Graves' disease.<sup>21</sup> The observation continues to be a curious feature of Graves' disease but little more is known of its meaning.

Many years ago patients frequently died of severe hyperthyroidism. Pathologists reported<sup>22-24</sup> extensive lymphocytic infiltration of skeletal muscle, cervical sympathetic ganglia, heart muscle and diaphragm. Dudgeon and Urquhart<sup>24</sup> and Naffziger<sup>25</sup> compared these changes to those seen in myasthenia gravis; the profound muscular weakness common to the advanced stages of both of these diseases came to mind. Persistence or enlargement of the thymus in Graves' disease was pointed out by Warthin<sup>20</sup> and many others.<sup>21</sup> Lymphadenopathy also was not uncommon. Why lymphoid hyperplasia

occurs in Graves' disease has never been explained. It is of particular interest that Rawson<sup>16</sup> has shown that lymph nodes or the thymus gland, when incubated with TSH, inactivate this substance, whereas no other tissues except those of the thyroid gland have such a capacity. It seems possible that lymphoid hyperplasia may be a method instituted by Nature to counteract Graves' disease.

It has long been recognized by the surgeon that numerous rather subtle features further characterize Graves' disease. Presumably because of the reaction within the thyroid gland, the strap muscles lying in apposition to the capsule of the gland have a tendency to be adherent; this is in all probability related to the lymphocytic infiltration of the thyroid. Muscles not in immediate proximity to the thyroid gland very often appear somewhat gray and friable. The grayness and crumbly quality of the thyroid as sometimes seen in patients with Graves' disease are manifestations of the degree of lymphocytic infiltration of the gland. Upon recognizing these features the surgeon is usually a little less radical when performing thyroidectomy because experience has taught that it is in such patients that one will ultimately find postoperative hypothyroidism or myxedema. It is most likely that the natural processes of cure are advanced in such patients.

#### NATURE OF THE THYROID HORMONE

Until recent years it was assumed that the thyroid hormone was thyroxine and that this was the ultimate product of the thyroid. As various methods of chromatography of iodinated compounds became available, triiodothyronine was discovered in the circulation of man and animals.<sup>26</sup> When it was synthesized and administered to man and animals it was found that this material increased the metabolism in a few hours as compared with the action of thyroxine which required days. Many years ago Plummer<sup>6</sup> postulated that the thyroid gland in Graves' disease produced a thyroid hormone that was somewhat different than the one usually produced by the normal gland and that this product was the cause of the symptoms of Graves' disease. Since this theory was suggested many years ago, it has hovered in the minds of many persons, but with skepticism. The theory was revived when triiodothyronine was discovered but there is still no proof that this substance is responsible for the clinical symptoms

of Graves' disease. It has been thought by some that triiodothyronine might be *the* hormone and thyroxine merely a precursor of it.<sup>27</sup> Because triiodothyronine disappears from the circulation quite rapidly as compared with thyroxine, the rather small amounts of triiodothyronine de-

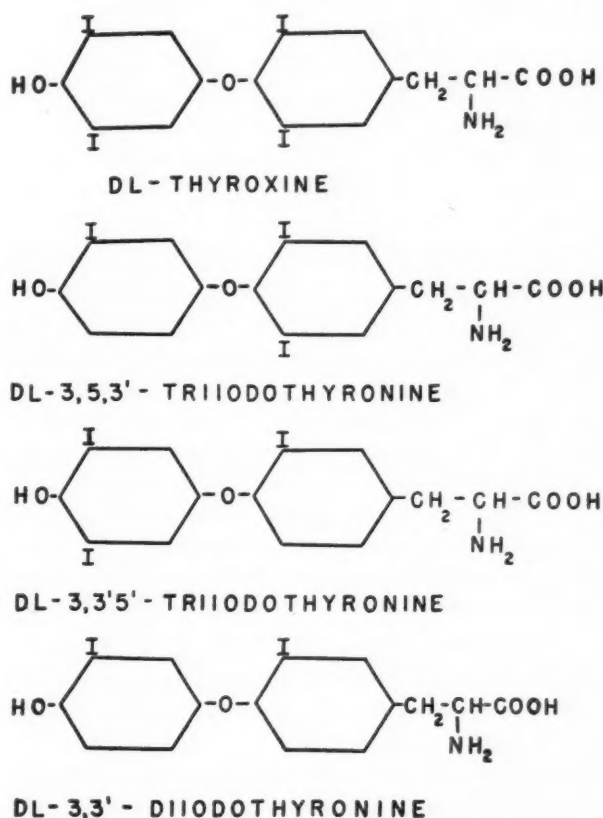


FIG. 4. Iodinated compounds known to be present in the blood and to have high metabolic activity.<sup>50</sup>

tected in the circulation may be of considerable significance. Recently Roche has described additional compounds detectable in the serum which presumably have a high biologic activity and are more active hormones than thyroxine. (Fig. 4.)

In patients given therapeutic doses of radioactive iodine, triiodothyronine was found more consistently among patients with higher degrees of hyperthyroidism.<sup>28</sup> Triiodothyronine was discovered in the circulation only a few hours after administration of I-131, before radiation effects could be detected. This compound appeared in the serum sooner than thyroxine and during the very early hours was more abundant than thyroxine, indicating that triiodothyronine was probably not a precursor of thyroxine.<sup>29</sup>

Considerable speculation may be raised in connection with the part played by the liver in



the pathologic physiology of Graves' disease. It has been observed<sup>30</sup> that 50 per cent of triiodothyronine may be found in the liver within five minutes after injection. It has also been shown that thyroxine and triiodothyronine, after passing through the liver, may be recovered in the bile in the form of a conjugate of glycuronic acid.<sup>31</sup> These substances pass to the intestinal tract where they are changed, partly reabsorbed and partly excreted.<sup>32</sup> The importance of this cycle in the normal human subject and in the patient with Graves' disease is still obscure.

It is well known that the thyroid hormone serves to increase the oxidative processes in tissues. It is clear that in the subject with Graves' disease the rate of conversion of iodide to thyroxine or thyroxine-like compounds and their release into the circulation is far more rapid than occurs in the normal subject. Thus an excess of the hormone may be the explanation for the increased metabolic activity of the various tissues. On the other hand, it is possible that there may be some differences among various persons in the response of the tissues to the hormone. It has been noted not infrequently that patients with progressive exophthalmos accompanied by a tendency toward hypothyroidism may require doses of thyroid several times greater than that usually necessary to bring hypothyroidism to a euthyroid state. These patients seem to tolerate unusually large doses of desiccated thyroid and are persons who at one time had had the hyperthyroidism of Graves' disease, indeed, still have Graves' disease as manifested by a persistence of the eye symptoms. It might be that the failure to respond to thyroxine is a mechanism which afforded protection from a previously overactive thyroid.

#### MANUFACTURE OF THYROID HORMONE

The considerable information now available regarding synthesis of iodinated compounds by the thyroid is of value in the application of therapeutic measures for hyperthyroidism. Iodine and tyrosine are the precursors of the thyroid hormone. Iodine is absorbed into the blood stream as iodide and arrives in this form at the thyroid; here the iodide is trapped by the thyroid cells. To form an iodinated organic compound it is necessary to convert iodide to iodine. This oxidation process immediately precedes attachment of the iodine atom to the 3- and 5-positions of the tyrosyl group. The thyroid gland has the capacity to trap iodide in

concentrations far greater than the level in the circulating blood but its capacity to store iodine in organic molecules is infinitely greater. Evidence<sup>33</sup> suggests that mono- and diiodotyrosine serve as a holding mechanism for iodine. A lack of agreement exists as to just how the thyroxine molecule is put together. The basic organic structure of the thyroid hormone is that of thyronine. The most biologically active iodinated organic compounds are the thyronines. There may be some uncertainty as to whether diiodotyrosine undergoes condensation to produce thyroxine or whether the thyronine base is directly iodinated. In any event, the bulk of the finished product is thyroxine which is bound to protein in the form of thyroglobulin and is stored in the follicle. De Robertis<sup>34</sup> has demonstrated the presence of a proteolytic enzyme which has to do with reduction in size of the thyroglobulin molecule and participates in the release of thyroxine. Presumably it is TSH which activates this enzyme and thus effects the appearance of intracellular droplets in the cytoplasm of the thyroid cell.

In some recent observations<sup>35</sup> it has been shown that the lymphatic pathways leading from the thyroid gland are important pathways of exit for the thyroid hormone. Administration of TSH into the thyroid artery causes a rapid rise in the amount of radioactivity in these pathways leading from a thyroid gland containing radioactive iodine, and this increase appears to be in the form of a protein molecule rather than as thyroxine *per se*.

#### ANTITHYROID COMPOUNDS IN TREATMENT OF GRAVES' DISEASE

If in any way the steps in production of thyroid hormone are interfered with, the output of TSH by the anterior pituitary gland is increased. A resulting increase occurs in the size of the thyroid gland in an effort for that gland to function in a way that it cannot. Thus a lack of iodine in the diet can result in hypertrophy.

Certain chemical compounds, when given in large enough quantities, interfere with the production of thyroid hormone. The resulting deficiency is followed by enlargement of the thyroid gland. These antithyroid substances are therefore regarded as having a "goitrogenic" effect.

During the last two decades a large number of antithyroid substances have been discovered. These substances act in different ways to prevent

the synthesis of thyroid hormone. One group of antithyroid substances, which includes thiocyanates and perchlorate, interferes with the trapping of iodide by the thyroid cells. This, in a sense, may be regarded as a competition for iodide space since this antithyroid action may be overcome by giving large doses of iodine.

Thiouracil and related compounds (thiocarbamides) inhibit the conversion of iodide to iodine. Thus these compounds block the synthesis of thyroid hormone at a step higher in the synthesis than the level at which thiocyanate is effective. Under such circumstances iodide is temporarily held at the level of trapping but it will not remain in large quantities because it does not become organically bound. Mercaptoimidazole acts in a similar manner. Certain aromatic compounds such as sulfonamides interfere with the synthesis of thyroid hormone by blocking the iodination of tyrosine.

The various compounds mentioned exhibit their action as long as the material remains at an effective level in the blood. The rates of destruction or excretion of these substances are variable in different species of animals and among individual human subjects. Propyl thiouracil, one of the common agents used for controlling hyperthyroidism, should be administered faithfully every six or eight hours to maintain continuous antithyroid action. When satisfactory therapeutic results are not forthcoming the effectiveness of the drug may be tested by giving radioactive iodine and measuring the degree and duration of the blocking effect. In some instances a failure of the blocking effect may be due to irregularity in taking the drug.

Because the thiouracil compounds block the synthesis of thyroid hormone, they have little effect on the thyroid hormone already bound to protein and stored in the follicles. Following the institution of such therapy there is often a delay in clinical improvement until the stored hormone has been depleted.<sup>36</sup> In Graves' disease the thyroid gland is usually seriously depleted of iodine and, if the gland is in such a state when therapy is instituted, clinical improvement exhibited by the patient is usually rather prompt. On the other hand, recent administration of large doses of iodide provides an abundance of stored organically-bound iodine in the gland. The result is a delay before the output of thyroid hormone is diminished, even if no further iodine is admitted to the gland. Although iodine administration has considerable additive thera-

peutic effect when administered simultaneously with thiouracil compounds, for the reasons indicated it is sometimes wise to institute thiouracil therapy somewhat in advance of iodine therapy, making sure that the patient is not only reliable but also punctual in taking the medication and that the dose of the drug selected is effective.

Thiouracil compounds have been used as a definitive form of therapy for Graves' disease. By administering such drugs for long periods of time and ultimately reducing the dosage slowly, some patients have sustained a permanent remission.<sup>37</sup> The most serious objections to this therapy are (1) the prolonged period of medication, (2) the occasional toxic reactions to the drugs, (3) the frequent tendency for recurrence of hyperthyroidism following discontinuance of the drug, and (4) the uncertainties arising from observations on the production of tumors in rats by prolonged therapy with thiouracil compounds.<sup>38</sup> It is generally felt that this method of therapy is most effective in patients with Graves' disease who have minimal enlargement of the thyroid gland. Further enlargement of the thyroid during treatment is usually not observed until the patient has reached a euthyroid state and is tending toward hypothyroidism.

#### SURGERY IN TREATMENT OF GRAVES' DISEASE

The prime objective of all preoperative care is reduction of the degree of hyperthyroidism.

For many years bilateral subtotal thyroidectomy was the sole satisfactory method for treating Graves' disease. With the introduction of preoperative iodine administration in 1922 by Plummer the mortality rate declined from approximately 4 per cent in the hands of the most experienced thyroid surgeons to a small fraction of 1 per cent. With the advent of antithyroid drugs a new tool became available for the preparation for surgery of patients with hyperthyroidism. In most clinics iodine administration for patients with relatively mild hyperthyroidism remains the preferred method of preoperative preparation. However, antithyroid drugs have made it possible to prepare for surgery many patients who would have been operated on at great risk if only iodine therapy had been used. For those patients who have moderate hyperthyroidism it seems most appropriate to institute preoperative preparation first with an antithyroid drug. After this therapy



has been in effect for some days, iodine therapy may be added. If the patient shows satisfactory improvement from iodine he may then be operated on within ten days or two weeks without prolonged administration of antithyroid. On the other hand, if iodine contributes relatively little to the patient's improvement, the antithyroid drug already instituted should be continued until the patient is ready for surgery. The objective of the surgeon in doing a bilateral subtotal thyroidectomy is to reduce the total functioning mass of the thyroid to a small fraction of the normal size. If each lobe of the thyroid is reduced to 2 to 4 gm., the recurrence rate is about 4 per cent.

The use of radioactive iodine as a therapeutic measure in Graves' disease is discussed elsewhere in this symposium and will not be considered here.

#### THE "CURE" OF GRAVES' DISEASE

When is a patient cured of Graves' disease? It is probably wrong to say "once Graves' disease, always Graves' disease."

It has been commonly thought that subtotal thyroidectomy is effective in curing Graves' disease not only because much of the site of origin of thyroid hormone is thereby removed but also because its removal interrupts some type of vicious cycle so that the patient ultimately reverts to normal. This probably is true in many cases. Although these patients are presumably cured of hyperthyroidism and although their basal metabolic rate is within what is considered to be the normal range, a surprising number of them reveal emotional instability, nervousness and certain subtle characteristics which indicate that they still have Graves' disease. Most patients are quite pleased with their recovery because of the effects of a decided lowering of the metabolic rate. Often these patients have been given iodine in moderate amounts for indefinite periods because certain manifestations persist or because the surgeon was concerned about "recurrence." The fall of the metabolic rate and the dramatic improvement in the sense of well-being produced by iodine administration in Graves' disease is well known. It is less well recognized that after "cure" by subtotal thyroidectomy patients may be made to feel more at ease and will still demonstrate a decline in the basal metabolic rate to subnormal levels when iodine is given. (Fig. 3.) Indeed, Haines<sup>39</sup> and Rynearson<sup>40</sup> have described patients in a euthyroid state

whose condition could be converted to a myxedematous state merely by administering iodine. If a careful history is taken of patients who presumably have recurrent hyperthyroidism, it will often be found that the patient took iodine for a prolonged period following thyroidectomy. Shortly after discontinuing the iodine those symptoms began which prompted return to the doctor, with a subsequent diagnosis of recurrent hyperthyroidism.

Several studies have been made on the remnant of thyroid after thyroidectomy. Pemberton<sup>41</sup> reported regressive changes in six of seven patients one year and three months to eleven years and nine months after treatment. In two instances only one lobe had been removed. It is not clear whether regression to the normal state occurred. Roussy et al.<sup>42</sup> and Rienhoff<sup>43</sup> restudied two and four clinically cured patients, respectively, and found hyperplasia of the thyroid remnant in all. Presumably the longer the interval of years after the "cure" the greater the chance that the thyroid remnant has returned histologically to normal. It is doubtful that this can be clearly determined since therapeutic agents for hyperthyroidism change the histologic picture and are so readily available.

#### THE EXOPHTHALMOS PROBLEM

The ophthalmopathy of Graves' disease has been the subject of curiosity of many clinicians and investigators. Although much has been learned, crucial facts concerning the mechanisms of various eye signs have not been established. Eye signs should be divided into two groups:<sup>44</sup> (1) A number of signs are associated with the stimulated phase of Graves' disease, such as lid retraction, lid lag, globe lag, stare and tension of the orbicularis oculi; these manifestations are usually associated with the tension state accompanying Graves' disease and promptly disappear as hyperthyroidism is brought under control. (2) The second and most important group of eye manifestations are those associated with true forward displacement of the globe. Symptoms in this group consist of lacrimation, pain and a gritty sensation in the eyes; paresis or paralysis of some or all of the extra-ocular muscles and venous engorgement of the conjunctiva often appear. Malignant exophthalmos or progressive exophthalmos are the terms commonly given to this group of signs. Whereas the symptoms of the first group are associated only with the thyrotoxicosis of



Graves' disease, symptoms of the second group may be associated with thyrotoxicosis or with hypothyroidism.

Edema of the retrobulbar tissues as the cause of the second group of symptoms has been well accepted. From observations made at many operations to decompress the orbit, Naffziger<sup>25</sup> has pieced together the sequence of pathologic changes occurring in the orbit. As time passes edema is gradually replaced by connective tissue so that the exophthalmos becomes irreversible. Although this much of the mechanism is accepted, the cause of edema formation is still uncertain. It has been observed by Asboe-Hansen et al.<sup>45</sup> that there is a deposition of mucopolysaccharides within the tissue of patients with severe exophthalmos. A similar observation has been made in animals given pituitary extracts by Ludwig et al.<sup>46</sup> This material, being hydrophilic, is probably the reason for the formation of edema. The enlarging tissue mass behind the globe and within the bony orbit thus displaces the globe forward as a tambour.

The exophthalmos-producing substance (EPS) has been shown to be separable from TSH in anterior pituitary extracts.<sup>47</sup> The TSH fraction produces hyperplasia of the thyroid gland and the other substance produces severe exophthalmos in experimental animals. Thus TSH *per se* does not cause exophthalmos. The fact that EPS can be separated from TSH is not entirely unexpected inasmuch as progressive exophthalmos and hyperplasia of the thyroid may occur independently in clinical subjects.

In an effort to detect an EPS-like substance in the serum of patients with severe progressive exophthalmos the author has injected the serum of such patients into Fundulus, a small Atlantic minnow, which responds with exophthalmos when injected with pituitary extracts. Although final conclusions cannot be drawn at the present time, the serum of many of the patients does contain an EPS-like substance.<sup>48</sup>

Progressive exophthalmos should be regarded as a self-limiting process; it may proceed in one or both eyes for weeks, months or years but ultimately stops, sometimes unfortunately after use of the eye is lost. If the cornea receives adequate protection and the progression is sufficiently slow, compensation may occur so that loss of sight and motion of the eye does not occur in spite of extreme exophthalmos. In some patients rapidly developing pressure occurs behind the globe. The extra-ocular muscles restrain

the globe against the retrobulbar force, and in only a few weeks the patient may experience loss of function of the extra-ocular muscles, perforation of the cornea and panophthalmitis, without developing much exophthalmos. At any time during this course the cause may cease and the therapy being instituted is likely to be given undue credit. Unfortunately no effective therapy is known.

In keeping with the theory that TSH from the anterior pituitary gland is the cause of exophthalmos, it has been thought by many that large doses of desiccated thyroid might inhibit TSH and perhaps the progressive exophthalmos. From a practical standpoint this method of therapy is probably of little use in patients who are euthyroid or hyperthyroid; however, it should be acknowledged that desiccated thyroid is a mild diuretic and that loss of water from the tissues may be of some benefit. It is of considerable benefit if the patient is in a hypothyroid state. Large doses of desiccated thyroid may cause a temporary recession of  $1\frac{1}{2}$  to 2 mm. in the prominence of the eyes in a euthyroid patient. If the course of exophthalmos is plotted from very careful measurements made over a period of time, it can be seen that the slight improvement affords a little slack but that the progressive course usually remains the same.

Protection of the cornea to avoid drying and ulceration is of greatest importance. Because these patients experience much more difficulty and have the highest exophthalmometer readings in the early morning, sleeping upright is very helpful, just as elevation of the lower extremities is beneficial for edema of the feet and ankles. These maneuvers and many more are merely methods of modifying edema, thus protecting the eyes while the patient and his physician are waiting for the pathologic influence causing progressive exophthalmos to abate. Fortunately, few reach serious proportions. When progression of the exophthalmos becomes arrested, its reversibility is dependent on the proportional amounts of edema and connective tissue behind the globe. The former may be reabsorbed but the latter remains. It is the author's opinion that once this disease begins to abate there will be no further exacerbation as long as the thyroid activity remains quiescent.

Probably the most important physiologic principle that experience has taught in the management, or perhaps the avoidance, of progressive exophthalmos is the deleterious

effect of hypothyroidism. There are probably two reasons, if such factors have a bearing on the disease: (1) the storage of water in the tissues in hypothyroidism and (2) the possible stimulus to the pituitary. Patients who display any of the signs and symptoms mentioned among the second group of eye manifestations (lacrimation, photophobia, irritative phenomena, pain or diplopia) should be watched very closely following application of any therapeutic means for lowering thyroid function.

It has been said by some that patients with impending difficulties of the eyes should not be subjected to thyroidectomy.<sup>21</sup> In contrast, it has been the experience of many others<sup>49</sup> that correction of hyperthyroidism often is accompanied by permanent improvement of severe exophthalmos. The more recent literature contains many reports of progressive exophthalmos associated with normal or subnormal basal metabolic rates. The unique paradox often prompted the publication. A review of literature published before the turn of the century, when the mortality rates restrained the enthusiasm of the surgeon, revealed that most case reports of exophthalmos progressing to loss of vision were usually accompanied by severe hyperthyroidism. It has long been known that incidence of exophthalmos increases with the duration of Graves' disease.<sup>5</sup> If it is true that correction of hyperthyroidism may break some cycle that perpetuates the basic cause of the disease, this might serve as a further argument for not allowing this part of the disease to go untreated.

It has also been suggested that perhaps radioiodine, as a method for treating hyperthyroidism, might be somewhat more kindly to the eyes because of the slow readjustment from hyperthyroidism to euthyroidism. Progressive exophthalmos may, however, follow this form of therapy also. Thus at the present time it seems preferable to treat hyperthyroidism when it arises and face the problem of severe exophthalmos if and when it should arise.

Hyperthyroidism should be looked upon as one of the results of Graves' disease rather than the cause of it. It would seem that we should now be on the threshold of the discovery of the origin of this disease.

#### ADDENDUM

Since the appropriateness of certain terms was questioned in the early part of this publica-

tion, it should be acknowledged that the term "toxic nodular goiter," used frequently in this publication, may also be criticized by some readers. "Hyperfunctioning adenomatous goiter" should be regarded as an equally satisfactory term for the same disease.

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# Physiologic Considerations in the Genesis and Management of Nodular Goiter\*

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**T**HE immediate cause of simple goiter is failure of the thyroid gland to obtain a supply of iodine sufficient to maintain its normal structure and function. This failure is usually brought about by an absolute environmental deficiency of iodine; it may also be caused by factors which interfere with the availability of dietary iodine or which impose an abnormal demand on the thyroid gland."<sup>1</sup>

This admirable epitome of the problem to be discussed here is quoted from the memorandum of the Goiter Sub-Committee of the Medical Research Council (1944). It makes an excellent introduction to any consideration of the genesis and management of simple nodular goiter. The immense amount of goiter in the world today revealed by the World Health Organization conference<sup>2</sup> held in London in 1952 and the fact that practically all simple goiters become nodular with the passage of time, bringing with them a train of complications and disability, makes this subject one well worthy of study.

## ANATOMY

*The Follicle, the Lobule and the Lobe.* The fundamental secretory unit of the thyroid gland is the follicle, a spherical structure made up of a single layer of cuboidal cells with a basement membrane and covered with a rich network of capillaries. The follicle contains in its lumen a clear viscid substance, colloid, which in health usually contains stored thyroid hormone. The grouping and blood supply of these follicles is a matter of the greatest importance when one considers the evolution of nodules in the gland.

Twenty to forty follicles are bound together with connective tissue to form a lobule and groups of these are incorporated into disc-shaped lobes. A single artery supplies each lobule as has been demonstrated very clearly by Johnson<sup>3,4</sup>

who perfused the excised gland with warm saline solution via the inferior thyroid artery for thirty minutes or more. The result was that the gland became 'oedematous' and the swollen interlobular and interlobar septa showed up its structural pattern very clearly even to the naked eye. It is interesting that the lobular structure of the thyroid, which must be familiar to most workers in this field who are frequently looking at histologic sections of the gland, was for many years doubted. This was due largely to the work of Rienhoff,<sup>5</sup> who used the method of wax model reconstruction from serial sections to demonstrate the anatomic pattern of the gland. His work revealed one important fact, that there were no interfollicular cells in man, but the reconstructions gave the appearance of branching coral and he concluded that there was no evidence of true lobulation in the thyroid. As Johnson in his criticism of this work rightly points out, it is a mistake to draw too wide-reaching conclusions from one single method of study.

Groups of lobules are bound together to form what Johnson refers to as "structural lobes" and these are separated from each other by fine sheets of fibrous tissue in which run the blood vessels. These "structural lobes" are in turn bound together to form the anatomic lobes of the gland. Both anatomic lobes of the thyroid, together with the occasionally present pyramidal lobe and the isthmus, are built up in the same lobular fashion.

*The Blood Supply.* The blood supply of the thyroid comes mainly from the paired superior and inferior thyroid arteries which break up into many anastomosing vessels on the surface of the gland; branches of the arteries dip down in the interlobar septa to reach lobules and eventually follicles. The most direct way of studying the

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vascular supply of the thyroid is to inject the vessels of the excised gland, then carry out microdissections and also examine thin and thick sections of the injected tissue. There have been many workers in this field, probably the first being Anna Bégoune<sup>6</sup> (1844), who studied nodular goiters and showed that many nodules had a poorer blood supply than the rest of the gland. Major<sup>7</sup> in 1909, using injections, showed that the blood supply followed the lobular pattern of the gland, and in 1929 Wangenstein<sup>8</sup> noted that in the long-standing goiters found in cretins in de Quervain's clinic in Berne the inferior thyroid artery might equal in size the common carotid.

Many investigators have postulated and tried to demonstrate arteriovenous anastomoses in the thyroid vessels. Their existence appears likely when one considers the immense vascularity which may appear in both simple and toxic goiter. Modell<sup>9</sup> described arteriovenous shunts in the dog thyroid, using a silver impregnation technic, which occurred mostly in the smaller vessels. On the other hand, arterial anastomoses can be seen with the naked eye on the surface of the gland and they have also been demonstrated by injection technics within the gland substance.<sup>10,11</sup>

#### ETIOLOGY OF NODULAR GOITER

*Iodine Lack.* The most important factor in the production of a nodular goiter is of course lack of iodine, and in many parts of the world the dietary intake falls short of the basic daily requirement estimated at about 100 to 200  $\mu$ g. for an adult. In childhood and especially in puberty it is likely that a greater amount of iodine is necessary, and certainly in areas of endemic goiter enlargement of the thyroid gland very commonly first appears at puberty and may disappear spontaneously later. Where endemicity of goiter is great, for example, the foothills of the Himalayas in India and Nepal, the slopes of the Andes in Argentina, Switzerland and parts of Southern Ireland, there is one factor in common, namely, a very low iodine content in the water and food. The introduction of articles of food from outside the endemic area often leads to a lessening of thyroid enlargement and, as the ability to purchase such food is only found among the well-to-do, the biggest goiters are usually to be seen in the poorest people.

*Sex.* Although iodine intake in one particular area may be uniformly low, the incidence of goiter among persons may be far from uniform.

Women show thyroid enlargement much more commonly than men and this may be due to the repeated brief stimulation of the gland with each menstrual cycle and the more sustained demand made on the thyroid in pregnancy. The clinical observation of premenstrual increase in thyroid size has been well established but no good evidence of greater physiologic activity accompanying it has been noted.

*Goitrogens.* In ancient times goiter was thought to be due to the ingestion of some poison in the water<sup>12</sup> or diet<sup>13</sup> and many substances have been incriminated.<sup>14</sup> No known naturally occurring substance has been found which can produce a goiter when the iodine intake is adequate, but in instances in which the amount of iodine in the diet falls to critical levels the addition of one of the goitrogens may tip the scales in favour of thyroid enlargement.

*Water Pollution.* Pollution of drinking water with human and animal excreta has been known to precipitate goiter in low iodine areas. The pioneer investigations of McCarrison<sup>15-20</sup> at the beginning of the century first drew attention to the problem. He studied the incidence of goiter in a group of nine villages which make up Gilgit in the foothills of the Himalayas in Northern India. These villages, situated one below the other, all drew from the same water supply; as it descended the water became more and more polluted with human and animal excreta. A survey showed that eight of the nine villages showed a steadily increasing incidence of goiter corresponding to the increase of pollution. The one exception was a village which had an independent water supply from a spring. McCarrison filtered off the solid matter from the polluted water and twice daily gave himself and a group of army volunteers, who had been drafted to the district, 6 ounces of a suspension of this matter. In one-third of the group, including himself, goiter developed between the tenth and fifteenth day, reaching maximum size between the twenty-fifth and thirtieth day. The goiters all disappeared after the experiment was finished but, in the original paper, there is a photograph of McCarrison with an obvious diffuse thyroid enlargement. I can vouch for the fact that Sir Robert McCarrison has no goiter today. The iodine content of the water and food was low but did not itself lead to goiter, a fact which was clearly demonstrated by giving a control group of subjects the same polluted water after it had been boiled; in none of them did thyroid swell-

ings develop. Ten years later Marine and Lenhart described an epidemic of goiter due to water pollution but in their case the subjects were trout at a hatchery.<sup>21,22</sup> They found that thyroid hyperplasia occurred in these fish which were reared in tanks situated one below another, the effluent from a tank running down into the next and the degree of hyperplasia increasing in each successive tank.

**Calcium.** For centuries it has been pointed out that there is some association between goiter and drinking water which comes from an area of limestone or calcium carbonate.<sup>23-29</sup> Simple goiter in England is often called "Derbyshire Neck" from its frequent occurrence in that county. The geologic formation is largely carboniferous or mountain limestone which is cut into deeply by the rivers Derwent and Dove. In 1831 Boussingault<sup>30</sup> in Nouvelle-Grenade, or Colombia as it is now called, correlated the incidence of goiter with the geologic formation of the country and stressed the association of goiter with limestone formation. More recently Naughten<sup>31</sup> in Tipperary in Southern Ireland has remarked on the importance of the limestone of the Galtees and Slievenamon mountains as a factor explaining the distribution of goiter in a low iodine area. The various theories proposed to explain the goitrogenic action of calcium were reviewed by Taylor.<sup>32</sup> In the rat, maintained on a low iodine diet, he was able to show that added calcium carbonate increased the thyroid hyperplasia as demonstrated by increased thyroid weight, depletion of colloid and increased radioiodine uptake. Added calcium did not inhibit iodine absorption from the intestine and its effects could be completely prevented by adding iodide to the rats diet. Axelrad et al.<sup>33</sup> were unable to demonstrate the same effect in mice.

**Fluorine.** This halogen when present in excess produces a typical mottling of the tooth enamel in children and may also produce goiter. Wilson<sup>34</sup> showed it to be a factor in the Punjab of India and it has also been reported as an important factor in endemic goiter in South Africa.<sup>35,36</sup>

**Chloride.** Yet another halogen may be goitrogenic in the presence of a low iodine diet. In 1943 Sharpless and his co-workers<sup>37</sup> suggested that under suitable conditions the chloride ion might displace the iodide ion and lead to thyroid hyperplasia. This has recently been confirmed in animal experiments by Axelrad et al.<sup>38</sup> No

evidence has appeared so far that this is a factor in the production of goiter in humans.

**Foods.** The introduction of radioiodine in the investigation of thyroid function has provided such a sensitive method for measuring anti-thyroid substances that a wide range of articles appearing in the diet are now known to have goitrogenic properties, if only to a slight degree. Greer and Astwood<sup>38</sup> have pioneered the study and a comprehensive review of the subject was presented by Fertman and Curtis<sup>39</sup> in 1951.

The food receiving most attention so far has been cabbage, ever since Chesney<sup>40</sup> in 1928 discovered that rabbits fed almost exclusively on it developed large goiters; the work was confirmed by McCarrison.<sup>41</sup> Later Hercus, Purves<sup>42</sup> and Kennedy<sup>43</sup> in New Zealand showed that rape seed from another of the brassica family was a more powerful goitrogen. This led to an appreciation of thiourea as a goitrogen (Kennedy<sup>44</sup>) and subsequently Astwood<sup>45</sup> introduced thiouracil as a valuable therapeutic agent. Greer et al.<sup>46</sup> isolated the active goitrogenic principle from the rutabaga, 1,5-vinyl-2-thioxazolidone. The author knows of no well authenticated case in which cabbage or any other brassica has produced goiter in man, although it may do so in farm animals.

Soya bean is another goitrogen,<sup>47,48</sup> but since the list could be continued indefinitely the reader is referred to the authoritative review of Fertman and Curtis.<sup>39</sup> The importance of these substances in the diet is of more academic than practical interest.

**Drugs.** A number of drugs not employed primarily for thyroid therapy have been discovered to exert a goitrogenic action. Thiocyanate,<sup>49,50</sup> which was previously used in the treatment of hypertension, blocks the iodide-trapping mechanism of the thyroid without inhibiting binding of the iodine to protein and may thus in time produce a goiter; perchlorate behaves similarly.<sup>51</sup> Paraminosalicylic acid (P.A.S.), which is extensively used in conjunction with streptomycin for the treatment of tuberculosis, is a poor inhibitor of iodine binding but since it is used for prolonged courses of therapy may be goitrogenic.<sup>52</sup> Cobalt, which is of value for treating anaemia in uraemia, occasionally produces a goiter.<sup>53</sup> Resorcinol, which is often found in ointments applied to chronic ulcers, was discovered when used over a long period of time to lead to myxoedema<sup>54</sup> and it acts as a mild thyroid blocking agent.<sup>55</sup> The sul-



phonamides were shown by the Mackenzies<sup>56,57</sup> in Baltimore to inhibit thyroxine synthesis but fortunately these drugs are not often employed in such amounts as to cause significant change in thyroid function.

#### EVOLUTION OF NODULAR GOITER

*Natural History.* The natural history of thyroid enlargement in an area of endemic goiter has been often and closely studied; one of the clearest accounts is to be found in the exhaustive studies of Olesen and Taylor for the United States Public Health Service.<sup>58-61</sup> It must be remembered that different districts vary greatly in the severity of the endemic but in a typical area the thyroid becomes moderately enlarged in early childhood so that at the age of five some 25 per cent of boys and 33 per cent of girls present such an enlargement. At puberty the goiter is prominent but as time passes it is common for it to diminish in size in the male sex while persisting in the female. Puberty goiter has been regarded by some workers<sup>18</sup> as a physiologic rather than a pathologic enlargement since it reflects the enhanced demand made on the gland at this period and appears completely reversible. In the adult woman such a gland is liable to enlarge during each pregnancy and by the fourth decade is often discovered to have become nodular. These nodules may be of all sizes, most of them contain colloid and are subject to haemorrhage and cyst formation. The problem posed here is why does this long-standing overactivity of the thyroid always lead to the formation of nodules which in time replace the whole substance of the gland? In order to answer this question it is necessary to understand the pathologic physiology of prolonged iodine deprivation and the mechanisms which the body brings into use to combat it.

*Experimental Goiter.* The mechanism by which a low iodine diet induces thyroid hyperplasia has been intensively studied in the experimental animal and might be considered to take place as follows. An initial fall in the amount of circulating thyroid hormone (protein-bound iodine) could take place, although this has not in fact been measured. This in turn stimulates a raised secretion of thyrotrophic or thyroid-stimulating hormone (TSH) by the anterior pituitary.<sup>63,64</sup> An accompanying histologic change occurs in the pituitary gland after the elapse of months, with the appearance of "thyroidectomy cells" and decreased acidophilia (Griesbach<sup>65</sup>). This

increased output of TSH leads to thyroid hyperplasia. The possibility that in iodine deficiency the iodide-trapping mechanism is more sensitive, or that the effect of TSH on the thyroid follicles is potentiated, has been suggested by a number of workers.<sup>66-68</sup> Halmi<sup>69</sup> working with rats has confirmed this increased efficiency of the thyroid in accumulating iodide in iodine deficiency, in the absence of any signs of increased TSH production by the pituitary.

Most of the experimental work on the production of goiter with a low iodine diet has been done using rats. Many excellent accounts of short-term iodine deficiency have been noted. Money, Rall and Rawson<sup>70</sup> reported a marked increase in radioiodine I-131 uptake after forty-eight hours on a low iodine diet, reaching a maximum in some twenty days. This increased I-131 uptake was for some months not accompanied by any increase in the weight of the thyroid gland, although Maloof, Dobyns and Vickery<sup>71</sup> reported an increase in thyroid weight as early as the eleventh day on a Remington diet. Money et al.<sup>70</sup> suggested that increased concentration of I-131 by the thyroid reflected a decrease in the available "iodine pool" rather than an actual increase in iodine accumulation, in other words an increased specific activity of the labeled iodine.

In an attempt to follow the effects of long-term iodine deficiency in the experimental animal the author has maintained rats for two years on a low iodine diet (Irving and Simpson) and made serial observations on thyroid weight, I-131 uptake, size of follicles and formation of nodules, making autoradiographs of many of the thyroid glands after sacrifice of the animals. It was found that rats maintained on this diet, which provided about 1.6  $\mu$ g. of iodine a day, grew fairly normally but showed colloid depletion and decrease in follicle diameters. The radioiodine studies showed rapid uptake to a high level and rapid discharge, but this pattern remained practically unaltered from the twenty-first day to the twenty-fourth month. A wide variation in the size of the thyroids was noted but there was great uniformity in the histologic pattern. Nodules appeared from the fifth month in increasing numbers. They were of trabecular pattern and autoradiographically their iodine uptake was similar to the rest of the gland with one exception.<sup>72</sup> Axelrad and Leblond<sup>73</sup> (1955) have recently described a similar study and in a beautifully documented

account have classified the type of hyperplastic cell observed into three categories.

*Iodine Metabolism in Simple Goiter.* One of the best accounts of iodine metabolism in patients with simple goiter is that provided by Stanbury and his associates<sup>74</sup> as a result of their visit to an endemic area in Western Argentina in 1951. They investigated more than a hundred goitrous patients by determining their uptake of radioactive iodine, level of protein-bound iodine in the blood and urinary iodine excretion. They found that the I-131 uptake was greater and faster than in persons living in a district with normal iodine intake and that the urinary excretion of iodine was low while the renal clearance of iodine was unaffected by the most severe iodine depletion. The serum protein-bound iodine was rarely below the normal range. The addition of small daily supplements of iodine did not lead these persons back toward some hypothetical "normal" iodine content in their glands but the retention was proportional to the size of the supplement. One woman given 1.5 mg. of iodine a day developed frank hyperthyroidism, an example of the "Jodbasedow" or iodine-induced hyperthyroidism described by Swiss and German authors.<sup>75,76</sup> In our own clinic when patients who are not clinically hyperthyroid present an increased I-131 uptake and the possibility exists that they are iodine deficient, they are sent away for six weeks on a daily dose of about 1 mg. of iodide and again tested with radioiodine at the end of this period.<sup>77</sup> If hyperthyroidism is present they still present an increased uptake, but if they are iodine deficient they show a return to a normal pattern of I-131 excretion.

*Autoradiography.* The technic of autoradiography (or radioautography), that is, the exposure of a section of tissue to photographic emulsion so that the latter is blackened when radioactive material is present in the tissue, is of particular value in the study of goiter. It makes possible correlation between the histologic characteristics of any given area and its ability to concentrate iodine to protein or, in other words, manufacture the thyroid hormone. In our laboratory more than a hundred patients with various types of simple goiter have been investigated by this method and, since sections were cut through whole thyroid lobes using a sledge microtome, an overall picture of the glands' function is obtained. The clinical material was representative of most stages of nodular

goiter since sporadic goiter is relatively common in London and many persons from areas of endemic goiter in Southern Ireland come to this area of London for employment.

The method employed<sup>78</sup> was to admit the patient to the hospital, obtain a full case history and particulars of the family and of the districts where the patient had lived. A hundred microcuries of I-131 were given by mouth after a short fast, and the urinary excretion measured by collecting urine for forty-eight hours<sup>79</sup> as a measure of overall thyroid function. The neck was often scanned<sup>80</sup> with a collimated Geiger-Mueller tube<sup>81</sup> and then a thyroidectomy performed after 48 hours. The excised thyroid was weighed and a drawing made; slices were made through whole lobes and fixed in 10 per cent formol saline. After preparation for histology in the usual manner sections were cut on a sledge microtome and placed in contact with fine grain x-ray film in light tight boxes in a refrigerator. The films were developed at one, two and eight days and compared with the histologic preparations which were stained with haematoxylin and eosin.

The autoradiographs showed a patchy distribution of the isotope, intense blackening being confined to discrete areas not necessarily correlated with nodules and the remainder of the gland usually presenting little evidence of iodine uptake. This is in contrast to what is seen in the normal thyroid in which the blackening is usually scattered throughout the entire autoradiograph. A study of the histology showed that these discrete areas of iodine uptake were made up of groups of follicles of a smaller average diameter and greater uniformity of size than in the rest of the gland. It was also noted that the cell heights were usually tall, which is a good indication of activity, as shown by the work of Rawson. The diameters of 100 follicles in two axes at right angles to each other were measured in active and non-active areas, and it was found that the active follicles had average diameters of approximately one-third the inactive ones. The size of the active follicles was also much more uniform, whereas the inactive follicles had widely divergent diameters.<sup>82</sup>

When the autoradiographs of a large number of simple goiters were studied in conjunction with age, sex, family history, district of domicile, diet and clinical history of the patient it seemed possible to reconstruct the natural history of the evolution of nodular goiter and, for convenience,



five stages were chosen. It is not practicable to obtain serial biopsy specimens from any one patient to obtain a representative picture of the pathologic changes. It must be added that there are other possible interpretations of the autoradiographic findings.

*Stage I:* Diffuse enlargement of the thyroid was present which was soft and very vascular. The total radioiodine uptake was in excess of normal. To the naked eye the gland presented no nodules, and histologically the follicles were uniformly small and many contained colloid. Where the colloid was scanty, the cells were extremely tall and the blood vessels prominent. It was rare for this condition to require surgical treatment.

This diffuse hyperplasia resembles that seen at puberty, the gland being referred to as a puberty goiter.

*Stage II:* (1) Many thyroid glands showed small discrete areas of hyperfunction as indicated by blackening on the autoradiograph. These areas were made up of groups of small follicles and the groups were seen in every form, from a mere cluster of follicles to a clearly defined nodule. The blood supply to these areas was more liberal than to the rest of the gland. (2) On three occasions a solitary hyperactive nodule was encountered, the remainder of the gland showing practically no activity. It would appear that in all of these patients the thyroid hormone was being manufactured in this solitary area and apparently the mass of tissue was not sufficient to cause hyperthyroidism, since there was no clinical evidence of it and the urinary I-131 excretion fell within normal limits. This group appeared to form a close link with those hyperthyroid patients who have a solitary toxic nodule described clinically by Plummer<sup>83,84</sup> and confirmed with isotope technics by Cope et al.<sup>85</sup>

*Stage III:* The foci of intense activity described in the two preceding stages appeared to proceed inevitably to haemorrhage followed by central necrosis. It would appear that the very activity of these nodules, with the consequent increased vascularity, culminated in haemorrhage. It has been shown by an injection technic<sup>10</sup> that these nodules are supplied by vessels which may be giant vessels and others which are tortuous, dilated and sinusoidal.<sup>86,87</sup> Some of these vessels showed evidence of thrombosis with consequent necrosis of part of the nodule so that destruction may have occurred without frank haemorrhage,

as suggested by Johnson.<sup>88</sup> That the destruction was of fairly sudden onset was occasionally demonstrated by the autoradiograph which showed a nodule with a remaining rind of active follicles, a phenomenon first described by Dobyns and Lennon.<sup>89</sup>

*Stage IV:* With the passage of time more of the nodules were found to be incapable of taking up radioiodine. The final appearance of a nodule which had passed through an initial phase of activity followed by necrosis was one of complete inactivity autoradiographically. The nodule might be replaced by a single lake of colloid or new follicles of varying size might grow in it. Some nodules showed fibrosis and calcification.

*Stage V:* The multinodular goiter of the patient over forty years of age was the end result of this cycle of hyperplasia and destruction recurring many times in the gland. At first sight a section across the so-called pudding stone goiter presented a bizarre appearance, but closer inspection showed it to be made up of nodules representing the four stages described above.

As long ago as 1863 Virchow<sup>90</sup> pointed out that the first phase in the production of simple goiter was hyperplasia. It appears from this study that it first affects the thyroid diffusely, then becomes focal and as each focus becomes burned out, due to its own overactivity, others take over until the whole gland is composed of a mass of nodules.

*The Sensitivity of Follicles to TSH.* One major problem which consideration of the facts just cited immediately raises is why hyperplasia should pass from uniform and diffuse in puberty to focal at a later stage. The lobular blood supply clearly accounts for exposure of a functional group of follicles to the circulating TSH but it does not explain why one lobule undergoes hyperplasia while those round about do not. Variable blood flows in the lobular vessels might be induced by changes in vasomotor control or by intranodular shunts. It is possible that not all the cells of a target organ show the same sensitivity to the stimulating hormone, and Zondek and Leszynsky<sup>91</sup> have championed this theory in the case of the thyroid gland. They base some of their conclusions on the unequal response of nodules and paranodular tissue to triiodothyronine given by mouth. The actual volume of the cell exposed to the blood and therefore to TSH<sup>92</sup> may well be a factor and could account for the vicious circle of



hyperplasia which so often involves the thyroid nodule.

We have taken slices from freshly removed nodular goiters (excised from patients who have had a tracer dose of I-131) and maintained them in buffered Krebs-Ringer solution in Warburg flasks agitated in a water bath maintained at 37°C. Different concentrations of a commercial preparation of TSH have been added, and the discharge of I-131 from nodular and non-nodular areas compared. Only rarely has there been a significant difference in the two, probably because the surface area of cells exposed to the hormone is the critical factor.

Frequently in our own clinic nodular goiter has been seen in patients who had been brought up for the first years of their lives in an area of endemic goiter but had moved to a non-goitrous area later. Nodules have developed even in those who left the endemic area before puberty. Presumably prolonged low iodine levels are capable of producing a change in the follicular cells which is lasting.

*Congenital Nodular Goiter.* Congenital goiter is seen occasionally in areas where goiter is not endemic. Often the condition is familial and typically the patient appears hypothyroid or cretinous. In those persons investigated with I-131 there has been intense avidity of the thyroid for iodine, often accompanied by an equally rapid discharge of the isotope from the gland.<sup>93</sup> Chromatographic study of the blood has shown the presence of significant amounts of mono- and di-iodotyrosine, often with almost complete absence of thyroxine.<sup>94</sup> Mono- and di-iodotyrosine occur normally in the thyroid but not in the peripheral blood stream except after radiation changes induced by large doses of radioiodine.<sup>95</sup> It would appear therefore that these patients suffer from an inborn error of metabolism and that it is frequently inherited. For example, McGirr and Hutchison's<sup>96</sup> twelve patients were from five families of tinkers in Kintyre, Scotland in which there had been much intermarriage; Hubble<sup>97</sup> described two of four cretinous siblings with goiter in England, and Stanbury wrote of two brothers in Boston<sup>98</sup> and another two in Holland.<sup>94</sup> If Roche's theory<sup>99</sup> is accepted that the dehalogenases in the thyroid deiodinate the iodo-tyrosines before they reach the circulation, then presumably those enzymes are absent in these patients. The existence of examples in a number of countries suggests that this condition may have a wide distribution.

Most of the reported examples of patients with congenital nodular goiter have shown low intelligence or have been frankly cretinous. We have recently seen a young girl with this defect whose intelligence quotient was above normal.

*Recurrent Nodular Goiter of Childhood.* On rare occasions nodular goiter is encountered in a young child from a non-goitrous area and the histologic appearances of the tissue are not malignant, using the criteria of loss of differentiation, rapid growth and capsular or blood involvement. However, the nodules often show solid masses of follicular cells and occasional papillary infoldings. The striking feature of these goiters is that they recur after an adequate thyroidectomy and may require total thyroidectomy for cure. A good account of three such children is provided by Heptinstall and Porritt.<sup>100</sup> It is difficult to exclude the possibility of an extremely low grade carcinoma in all the examples reported so far, and the observation that thyroid extract by mouth slows up further nodule development is not incompatible with such a hypothesis.

The occurrence of nodular goiters in rat colonies kept in districts where there is endemic goiter was first described in Switzerland by Langhans and Wegelin<sup>101</sup> in 1919, and Wegelin<sup>102</sup> in 1927 recorded the presence of malignant lesions in such thyroid glands. They have also been produced in animals by giving a low iodine diet<sup>103,104</sup> so that it is not difficult to conceive of a similar genesis occurring occasionally in the human thyroid gland which for one reason or another is deprived of adequate iodine.

#### MANAGEMENT OF SIMPLE GOITER AND ITS COMPLICATIONS

The management of simple and nodular goiter depends on a proper clinical appraisal of the patient. The development of simple goiter before or during puberty is almost always an indication that iodine intake is inadequate. The method of adding iodine to the diet will depend on the social habits of the region, but the most universally acceptable method is that of adding sodium iodide to the domestic salt so that an additional 100 µg. of iodine are ingested daily. It has been stated that the daily consumption of salt is about 10 grams per head in many countries<sup>2</sup> and therefore food salt should contain 10 mg. per kg. In certain underdeveloped countries the addition of iodine to sweets for

schoolchildren or to flour may be more suitable. It is, however, important that the iodine be given in physiologic and not pharmacologic quantities and that it be continued indefinitely.

Goiter is commoner among women than men, both before puberty and after. The cause of this is unknown and clearly demands investigation. In women there has been shown to be a temporary stimulation of the thyroid during part of the menstrual cycle and also a more prolonged one during pregnancy. For this reason supplementary iodide should be increased in pregnant women.

Certain families show a predisposition to develop goiter but it is difficult to dissociate this from dietary factors and other factors consequent on the environment. It is interesting that certain families also show a tendency to develop hyperthyroidism.<sup>105</sup>

*Complications. Cosmetic:* A large goiter may be symptomless but cause acute embarrassment because it is unsightly.

*Pressure effects:* The first structures in the neck to be compressed by a goiter are usually the great veins. In time the whole blood supply from head and neck may return by collateral circulation of veins over the chest wall, and if not conspicuous they can be demonstrated by an infrared photograph. Very rarely a superior vena cava syndrome may be seen. The trachea may be pushed to one side by an enlarging lobe or posteriorly by a bulky isthmus. Further thyroid enlargement may lead to compression of the walls from side to side resulting in a scabbard trachea and softening of the cartilaginous rings by chondromalacia. The result of this is dyspnoea on exertion and later at rest. Usually the patient finds that at night she can only breathe comfortably lying in one particular position and often uses an increasing number of pillows. Some of the cysts in a multinodular goiter are capable of changing size rapidly or may be the seat of haemorrhage with resulting acute dyspnoea. Dysphagia is surprisingly uncommon.

Almost every structure in the neck may be pressed upon by an enlarging goiter; certainly the carotids are often displaced laterally and sometimes posteriorly. The sympathetic chain is particularly susceptible to injury, and the author has seen a patient in whom Horner's syndrome developed overnight from haemorrhage into a nodular goiter.

*Toxic:* A proportion of nodular goiters even-

tually become toxic but it is impossible to estimate how many. A survey in England in 1928<sup>106</sup> suggested that the mortality from hyperthyroidism was greater in certain areas in which goiter was endemic, but more evidence is really needed on this point.

*Malignant:* It has been accepted by pathologists for a great many years that the incidence of cancer of the thyroid is higher in areas of endemic goiter. That this is in fact so was well demonstrated by Wynder<sup>107</sup> who quoted the death rate figures for cancer of the thyroid in the canton of Zürich from 1906 to 1945 and related these to the use of iodised salt.

Deaths (per 100,000)	Men	Women	Iodised Salt Used
1906 to 1915	2.04	1.43	1923, 18%
1916 to 1925	2.12	1.59	1930, 53%
1926 to 1935	1.40	1.74	1940, 55%
1936 to 1945	0.65	0.94	1950, 95%

Doniach<sup>108</sup> compared the mortality figures for malignancy of the thyroid in England and Switzerland. The population of England and Wales is almost exactly ten times that of Switzerland (44,300,000 and 4,300,000) but the death rate for carcinoma of the thyroid in the two countries is practically the same. In other words Switzerland with its endemic goiter had ten times as many deaths from cancer of the thyroid.

*Mental:* Cretinism occurs in areas where goiter has been endemic for a long time.<sup>109</sup> McCarrison pointed out from his work in Northwest India that in areas of great endemicity the mother who showed marked hypothyroidism was more likely to give birth to a cretin. The World Health Organization Study Group<sup>2</sup> in 1951 concluded that feeble-mindedness, apart from cretinism, rises distinctly in incidence in areas of endemic goiter. Educability is also lowered, with resultant economic loss. They did not feel, however, that the statistical evidence presented to them showed a significant correlation between the incidence of deaf-mutism and endemic goiter.

#### TREATMENT OF SIMPLE GOITER

The treatment of simple goiter has already emerged in the preceding account of its occurrence, development and investigation, so that it only remains here to summarize the findings.



**Supplemental Iodine.** Simple goiter is simply prevented by ingestion of an adequate amount of iodine daily, the amount varying with the age and sex of the individual, the type of diet and the calcium content of the water. These variations are not great and fortunately there is a very wide gap<sup>110</sup> between the probable range of human requirements (say, 50 to 200  $\mu$ g. daily) and the amounts likely to do anyone any harm. If the daily consumption of salt is estimated at 6 gm. and half of this is in the form of table salt, the addition of one part of iodine to 50,000 of salt would yield a supplement of about 50  $\mu$ g. daily. In the United States the amount added is about ten times this and in New Zealand about five, and experience extending up to twenty years has shown this addition of iodine to be safe. If the salt is kept dry, addition of sodium or potassium iodide gives a stable mixture but, under adverse conditions of moisture, heat and sunlight, potassium iodate offers a more constant supply.<sup>111</sup> Methods of adding iodide or iodate to crude salt, which is of course still used in many countries, have recently been evolved.<sup>112</sup> Murray and Pochin<sup>122</sup> have shown, using labeled sodium iodate in man, that the uptake by the thyroid is only 10 per cent less than when using sodium iodide.

**Desiccated Thyroid and Thyroxine.** The effect of giving thyroid substance to a normal person is to cause a reduction in radioiodine uptake.<sup>113</sup> In the iodine-deficient human thyroid the giving of thyroid produces a rapid fall in uptake which may take more than two weeks to be complete and shows wide variations in individual response.<sup>74</sup> This rate of decrease of iodine uptake could not be entirely accounted for by the iodine contained in the desiccated thyroid. Greer and Astwood<sup>114</sup> in 1953 described their experiences giving thyroid to patients who had simple goiter and they claimed marked regression of the gland size. In our own clinic during the last five years a number of patients with simple goiter have received sodium L-thyroxine in 0.2 mg. to 0.3 mg. doses daily. This synthetic thyroxine is more uniform in activity and iodine content than dried preparations of the gland. The results have been very variable and often disappointing. Smooth enlargement sometimes regressed well, nodular enlargement much less well, but there was usually marked softening in the consistence of the gland which made it difficult to estimate changes in size.

**Surgery.** The role of surgery in management

of nodular goiter is for the most part the relief of obstruction in the neck, mainly of the trachea and great veins. Often the goiter extends into the superior mediastinum but, carrying as it does its blood supply with it, it is usually easy and safe to remove it by the cervical route. Rarely the sternum has to be split. Thyroidectomy is also indicated when a malignant change is suspected, when toxic nodular goiter is present and finally for cosmetic reasons.

The incidence of malignancy has varied widely in reports from different clinics<sup>115-118</sup> but as Crile<sup>119</sup> has rightly stressed such figures reflect the selection of non-toxic goiters for operation by a particular surgeon and are not at all representative of the percentage of goiters that are malignant. The figures of Vanderlaan<sup>120</sup> and Sokal<sup>121</sup> are probably as much an understatement of the problem as the foregoing ones exaggerate it.

The reasons to suspect that a nodular goiter is malignant vary according to the age group. In young patients a solitary thyroid nodule, especially if there are in addition palpable lymph nodes in the neck, suggests a papillary carcinoma. In the older patient, a sudden increase in size of a long-standing goiter, pain, paralysis of a recurrent laryngeal nerve or evidence of metastasis are the main pointers toward malignancy. Differential diagnosis is difficult when there has been recent haemorrhage into a nodule or when there is an attack of de Quervain's giant cell thyroiditis.

The relief of obstruction by thyroidectomy in a simple nodular goiter is only the first stage in the treatment of the patient since often the same factors which led to the goiter are still at work. In addition, the sudden removal of much thyroid tissue from a gland already working under stress reduces still further its capacity to provide a normal supply of thyroid hormone. The author has found it necessary to prescribe sodium L-thyroxine or desiccated thyroid to most of post-operative patients for periods of one to five years and, in a few, indefinitely.

#### CONCLUSIONS

Simple goiter, with rare exceptions, can be prevented by a daily intake of about 200  $\mu$ g. of iodine in the diet. Before and during puberty the changes in the thyroid are usually reversible if a daily supplement of about 100  $\mu$ g. of iodine is given; with increasing age the changes become irreversible as the overall hyperplasia becomes



focal in distribution. After thirty years, nodules have appeared and bring with them a train of complications which can inflict a heavy burden on the medical services of the country. A preventible disease ought surely to be prevented.

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# Physiologic Concepts in the Genesis and Management of Thyroid Tumors\*

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IT has long been thought that normal physiologic mechanisms might be involved in the development of pathologic changes. In an endocrine tissue like the thyroid in which tumors have developed, such a relationship appears to exist. Much data have been collected which demonstrate similarities between normal and neoplastic thyroid tissue. With the establishment of these physiologic mechanisms in thyroid tumor development and maintenance, a basis for a rational form of management has been developed. A consideration of these relationships in the genesis and management of thyroid tumors is the purpose of the present paper.

## EXPERIMENTAL STUDIES

Occasionally spontaneous thyroid tumors have developed in animals through known conditions of nature, for example iodine deficiency.<sup>1-3</sup> This has suggested<sup>1,4</sup> that the endemic goiter of iodine deficiency bears a close relationship to malignant tumors of the thyroid both in man and in animals.<sup>5</sup> Thyroid gland tumors have, however, been developed in laboratory animals in several ways. These techniques have produced thyroid neoplasms in a far greater incidence than has been reported to occur spontaneously.<sup>1,6-10</sup> Not only hyperplasia<sup>11,12</sup> but also thyroid adenomas were reported in rats maintained on iodine-deficient diets.<sup>12-14</sup> The addition of iodine to such diets caused a decrease in the previously enlarged gland and reversed some of the changes considered intrinsic to true neoplasm formation.<sup>14</sup> Other structural changes induced by iodine deficiency in rats were considered more advanced and were not reversed by the addition of iodine.<sup>14</sup> In cases of prolonged iodine deficiency, under conditions in which the dietary intake and the iodine stores of the thyroid are less than the normal needs for thyroid hormone production, there is decreased

formation of thyroid hormone. This in turn leads to increased secretion of the thyroid-stimulating hormone (TSH) from the pituitary. It is this continued stimulation of TSH which actually induces hyperplasia and adenoma formation in the thyroid.

Goitrogenic agents of the thiouracil type induce thyroid hormone deficiency by virtue of their ability to block the conversion of inorganic iodide to organic iodine. These agents do not interfere with the collection of inorganic iodide by the thyroid. The resulting thyroid hormone deficiency leads to increased secretion of TSH from the pituitary as manifested not only by thyroid growth<sup>15</sup> but also by pituitary basophilia.<sup>16</sup> The basophilic cells of the pituitary are considered to be the source of TSH. It has been demonstrated<sup>17-19</sup> that thyroid powder or DL-thyroxine reverses thyroid hyperplasia or pituitary basophilia. Continuous stimulation of the thyroid gland following prolonged ingestion of the goitrogenic agents, thiourea, thiouracil, methyl thiouracil, propyl thiouracil and brassica seed (allyl thiourea),<sup>20</sup> leads to formation of adenomas in mice<sup>21-26</sup> and rats.<sup>15,27-33</sup> Feeding rats with a brassica seed diet or with the other compounds for short periods of time results merely in goiter formation.<sup>34</sup> Continual exposure to these agents results, however, in thyroid tumor formation.<sup>35</sup> Such thyroid tumors formed after prolonged goitrogen ingestion have not been limited to the thyroid but have metastasized to the lung<sup>17</sup> and have been transplanted into other animals.<sup>36</sup> Many of these transplanted thyroid tumors have demonstrated ability to grow only in thyroid hormone-deficient recipient animals.<sup>33,36</sup> In such an environment there would be an increased amount of TSH which could promote growth of the implanted tumor tissue. This is further evidence for the proposed theory that decreased availability of thyroid

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hormone after goitrogen ingestion leads to increased TSH secretion and the latter maintains tumor growth. Ultimately, such transplantable thyroid tumors may grow without dependence on TSH stimulation.<sup>37</sup>

In addition to an iodine-deficient diet and agents which prevent the conversion of iodide to organic iodide, reduction in the amount of thyroid tissue, usually by radiation, may also produce a thyroid hormone deficiency. Thyroid gland tumors were produced after doses of radioactive iodine which did not completely thyroidectomize mice.<sup>38</sup> This would suggest that some viable thyroid tissue must have remained to be acted upon by the increased amounts of TSH which followed the production of thyroid hormone deficiency.<sup>39</sup> Larger doses of radioiodine failed to produce thyroid neoplasms but did result in tumors of the anterior pituitary gland<sup>38,40,41</sup> and of the trachea. Tumors of the thyroid, approximately half of which were malignant, were also observed in rats given large doses of radioactive iodine.<sup>15</sup> However, while radioactive iodine will reduce the amount of thyroid tissue and consequent thyroid hormone deficiency, the ionizing radiation of this isotope may also be carcinogenic. The normal thyroid epithelium of those rats which harbored cancer was not unusually active as indicated by cell height, colloid content of vascularity, which suggested that there were no unduly high levels of TSH following the administration of a large single dose of I-131.<sup>15</sup> However, a depressing effect of two transplantable thyroid tumors on the weight of the host's thyroid during propylthiouracil ingestion has been reported.<sup>42</sup> This would be consistent with the formulation<sup>43</sup> that thyroid tissue may inactivate TSH. Thus it is possible that<sup>42</sup> a sufficient amount of thyroid tumor may inactivate the increased amounts of TSH attendant upon propylthiouracil ingestion. It is interesting that these transplantable tumors concentrated very little I-131 and grew more quickly in rats receiving propylthiouracil, presumably due to increased amounts of circulating TSH.<sup>42</sup>

Although malignancies of the thyroid gland have been reported in animals<sup>17,18,44</sup> receiving goitrogens alone, the incidence of malignancy can be increased by chemical carcinogens or ionizing radiation in association with the modalities for producing a decreased amount of thyroid hormone. Thus carcinoma was produced in rats<sup>28</sup> receiving both thiourea and 2-acetyl-

aminofluorene, while only adenomas were produced when the carcinogen was omitted. No thyroid tumors were noted in rats<sup>33</sup> after the administration of 2-acetylaminofluorene alone, but the addition of a goitrogen or partial thyroidectomy was required to produce a thyroid hormone deficiency with the associated increased secretion of TSH from the pituitary. Although methyl thiouracil was somewhat carcinogenic for the thyroid, this action was enhanced by the addition of radioactive iodine.<sup>44</sup> In the production of thyroid neoplasms there may be promoting factors, like an increased secretion of TSH, and initiating factors like a chemical carcinogen or ionizing radiation.<sup>32,45</sup>

Almost every histologic type of thyroid tumor noted in man has been simulated by prolonged thiouracil administration to rats.<sup>46</sup> It is interesting how many morphologic and functional similarities there are between experimentally induced thyroid gland tumors in laboratory animals and the spontaneously occurring neoplasms in man. Functional studies of thyroid tumors experimentally induced by antithyroid drugs suggest that although such neoplasms have physiologic similarities to normal thyroid tissue, there are distinct differences. There seemed to be no gross morphologic correlation between follicular diameter, cell height, colloid staining and the concentration of I-131 in tumors after thiouracil,<sup>46</sup> although the most rapidly growing tumor had the least ability to concentrate I-131.<sup>47</sup> In general, thyroid tumors collect less I-131 than normal thyroid tissue<sup>46-48</sup> and this has its counterpart in human thyroid tumors. This is true not only for total I-131 collection but also for the thyroid:serum radioiodide ratio.<sup>48</sup> Nevertheless, the thyroidal chemical compounds were qualitatively the same in mouse thyroid tumor and host thyroid.<sup>49</sup> The dependence of iodide concentration in thyroid gland tumors on physiologic mechanism was demonstrated by the decreased thyroid tumor:serum radioiodide ratio after hypophysectomy,<sup>50</sup> although exogenous TSH has been reported<sup>42</sup> to have an equivocal effect on thyroid tumor weight.

It can be concluded that thyroid gland tumors may be produced by agents which induce a deficiency of thyroid hormone. This in turn leads to increased secretion and action of thyrotrophin. For the stimulatory action of the latter, some viable thyroid tissue must remain. Although the promoting action of thyrotrophin is necessary for the formation of thyroid gland

neoplasms, initiating or accelerating factors may contribute to the development of such tumors. Functionally, the experimentally induced thyroid gland tumor has certain properties which are similar to normal thyroid tissue and other properties which are different from the non-pathologic gland.

#### GENESIS OF HUMAN THYROID NEOPLASMS

There are many observations made in connection with human thyroid gland tumors which indicate that the physiologic mechanisms operative in the experimental animal are similar to those in man.

Benign tumors of the human thyroid gland have been considered<sup>51,52</sup> to represent differences from normal thyroid glands in the degree of growth, differentiation, reversion and encapsulation. It was not thought<sup>52</sup> necessary to invoke an embryologic defect to explain a tumor like the "fetal adenoma." Nodules of the thyroid were conceived<sup>53</sup> to develop as a result of involution of previously diffuse thyroid hyperplasia, of the sort which occurs in hyperthyroidism. The latter condition with stimulated thyroid glands may be the result of increased TSH action on the thyroid.

It has been suggested<sup>1,54</sup> that there is a demonstrable relation between nodular goiter and carcinoma of the thyroid gland in areas of iodine deficiency.<sup>52</sup> Others,<sup>55-57</sup> however, have believed that this relationship was more apparent than real inasmuch as those patients coming to operation for non-toxic goiters were a highly selected group of cases. It has been reported<sup>57</sup> that less than 1 per cent of unselected nodular goiters are malignant. To some,<sup>56</sup> cancers of the thyroid gland in man are malignant from the onset and do not arise from a pre-existing benign or hyperplastic phase.

Recently, it has been reported<sup>58</sup> that the death rate from thyroid cancer in endemic goiter areas was almost ten times greater than the average for the United States. In humans, as in animals, the growth of the thyroid gland presumably is due to decreased thyroid hormone formation and release, and the consequent increased secretion of TSH. If increased TSH action is important in the production and maintenance of thyroid tumors, it would be expected that measures to decrease TSH secretion would decrease the size or incidence of thyroid tumors. Correction of iodine deficiency by iodine administration has not only decreased the incidence of goiters but has also produced a decrease in the number

of thyroid tumors.<sup>1</sup> Thyroid hormone, which inhibits TSH secretion, has not only induced remissions of goiter but has also caused decrease or disappearance of both single and multiple nodules.<sup>59</sup>

As yet no conclusive evidence has been reported for the production of thyroid neoplasms in man either by the ingestion of known goitrogens or following the reduction in amount of thyroid tissue either by surgery or radiation. Since it is difficult to administer sufficient doses of antithyroid drugs for long enough periods of time to induce a prolonged state of thyroid hormone deficiency, it may not be possible to reproduce knowingly the development of thyroid neoplasms by goitrogen ingestion, as can be accomplished in experimental animals. However, it may be that some of the goiters now considered to follow iodine deficiency or to be idiopathic may be the result of an unknown goitrogen. Patients who have been thyroidectomized by surgery, x-ray or radioactive iodine may not have shown an increased incidence of thyroid neoplasms either because all viable thyroid tissue has been removed or because patients have not been maintained in a state of thyroid hormone deficiency for sufficient periods of time with resulting increased secretion and action of TSH. In the state of prolonged iodine deficiency noted clinically, in which the reduced iodine intake leads to decreased circulating thyroid hormone, there may be a long period of increased TSH action.

#### PHYSIOLOGIC STUDIES OF THYROID TUMORS

The degree of function, as measured by the localization of I-131 of the various histologic types of thyroid cancer, has been demonstrated<sup>60</sup> by radioautographic localization of radioactive iodine in such tumor types.

Positive Autographs in Thyroid Cancer

Type	No. of Cases	No. Positive	% Positive
Papillary . . . . .	49	12	24
Alveolar and follicular . . .	56	38	68
Solid . . . . .	17	6	35
Hürthle cell . . . . .	13	3	23
Giant and spindle cell . . .	10	0	0
Anaplastic . . . . .	3	0	0
Unclassified . . . . .	2	1	50
	150	60	40



Although the demonstration of radioiodine localization in the various histologic types of thyroid malignancy is useful, two limitations must be considered from the point of view of treatment with radioiodine. Even those tumors bearing colloid-filled follicles which concentrate radioactive iodine do not demonstrate a uniform distribution of the isotope by radioautography. This may be related to the previous non-radioactive iodine stores of each follicle or perhaps there is some phasic activity of thyroid follicles. In addition many patients have tumors of more than one histologic type.

Functionally, malignant thyroid tumors bear certain similarities to and have certain differences from normal thyroid tissue. For example, radioactive iodine will localize in thyroid carcinoma but not be discharged by either carrier potassium iodide<sup>61</sup> or potassium perchlorate.<sup>62</sup> This suggests that the iodine is not present as iodide but is organically bound. In general thyroid carcinoma is less efficient than normal thyroid tissue in concentrating iodine.<sup>63</sup> Quantitative measurements of this localization of radioactive iodine in thyroid carcinoma reveal a rapid uptake<sup>64,65</sup> and release<sup>62,64,65</sup> of the isotope. Whether this represents a property peculiar to tumor tissue or merely reflects decreased non-radioactive iodine stores is difficult to ascertain at present. Although iodine is fixed in neoplastic thyroid tissue, its pathway of metabolism may be different from that in normal thyroid tissue. Not only the normally secreted thyroxine but also an abnormal iodinated compound has been identified<sup>66,67</sup> in the serum of patients with functional thyroid cancers. Thiouracil will not inhibit the collection of radioiodine by functioning cancers of the thyroid to the same degree as normal thyroid tissue<sup>43</sup> but this is sufficient to suppress thyroid hormone formation in overactive thyroid metastases and to cause a remission of hyperthyroidism.<sup>68,69</sup>

The localization of radioactive iodine in thyroid metastases is increased after thyroidectomy.<sup>63,70-81</sup> If normal physiologic mechanisms are operative, there would be a decrease in circulating thyroid hormone after thyroid ablation, with removal of the antagonistic effect on the secretion of TSH. Thyroidectomy would also remove a tissue which may be important in the inactivation of TSH. In any event, increased TSH is available for the stimulation of the tumor and promotion of iodine collection. In

addition, the more efficient normal thyroid tissue is no longer present to compete with neoplastic thyroid tissue from the point of view of iodine collection. This too would contribute to increased localization of radioiodine in the metastases after thyroidectomy.

The administration of antithyroid drugs to patients also increases the localization of radioactive iodine in metastatic thyroid carcinoma.<sup>71,72,74,77,80,82</sup> These drugs not only reduce thyroid hormone production by blocking the conversion of inorganic iodide to organic iodine compounds but they also have been reported<sup>43</sup> to potentiate the action of TSH. Under both circumstances there would be an increased TSH effect, with promotion of radioactive iodine uptake.

If thyroidectomy and thiouracil produce an increased uptake by metastatic thyroid tissue through the mechanism of increased TSH secretion or action, then administered TSH should have a similar effect. This has been demonstrated<sup>71,73,77-79,83,84</sup> by some although not observed<sup>85,86</sup> by others.

Although the data just cited suggest that alterations in pituitary function may be presumed to influence the localizing property of thyroid tumors for radioiodine, other observations<sup>62</sup> are difficult to reconcile with this concept. The administration of triiodothyronine or thyroxine did not reduce the discharge of radioactive iodine from thyroid tumors.<sup>62</sup> This, however, may merely be a problem of dosage, length or frequency of administration.

Although it is not readily apparent that physiologic mechanisms are operative in the genesis of thyroid tumors in man, the data are more convincing with regard to the role of such mechanisms in the maintenance of some function in these neoplasms. Procedures which produce increased secretion of TSH result in enhanced localization of radioactive iodine in thyroid tumors. Apparently, some aspects of the intermediary metabolism of thyroid tumors are similar to those at work in normal thyroid tissue, although distinct differences have been noted.

#### POSTSURGICAL MANAGEMENT OF THYROID CANCER

It should be stressed that the primary treatment of thyroid neoplasms is surgical and that medical management is supplementary rather than substitutive. With some understanding of the physiologic mechanisms operative in the

growth and maintenance of thyroid neoplasms, it is possible to formulate a plan of management based on the functional similarities and differences between normal thyroid tissue and thyroid tumors.

In practice, patients with inoperable metastatic thyroid cancer are thyroidectomized either surgically or with radioactive iodine. After thyroid ablation the antithyroid drugs are administered for approximately ten weeks, in doses of 600 mg. of the thiouracil derivatives or 60 mg. of mercaptoimidazole. The uptake in the metastases is determined by a tracer test performed forty-eight hours after discontinuing the drug. If the uptake is insufficient to permit treatment with radioactive iodine, the patients are retreated for many months with antithyroid drugs until there is sufficient uptake for treatment. At the Memorial Center, of sixty-six patients who have been thyroidectomized, treated with antithyroid drugs or both, thirty-nine have shown increased uptake in thyroid cancer. Only seven patients have received treatment doses of radioiodine without prior total thyroidectomy and/or treatment with antithyroid drugs. Most of these last few patients were treated because of the desperate clinical situation in an attempt to obtain some prompt relief.

Although thiouracil and mercaptoimidazole will induce a significant increase in radioiodine uptake in approximately 60 per cent of selected cases, there is no conclusive evidence that this is accompanied by a proportionate increase in the mass of tumor tissue. Therefore, more radiation can be delivered to thyroid cancer metastases from equivalent doses of I-131. It may be, however, that thyroidectomy will result in a significant increase in tumor size.

The relationship between uptake and radiation delivered from a given dose is linear but the relationship between iodide clearance by the thyroid neoplasm and radiation dose is exponential.<sup>87</sup> It is assumed that thyroid tumor clearance is the best index of functional activity. With this in mind, there will be some influence on the optimum time for treating a patient with radioiodine. At the low levels, an attempt should be made to increase uptake as much as possible, if the patient's clinical condition warrants it. This assumes that an increased uptake is not a reflection of increased tumor mass. At higher levels of uptake, further treatment with the antithyroid drugs may cause significant changes

in clearance but only a small increase in uptake and consequently only a small increase in radiation delivered. Thus it would be inadvisable to insist on the maximum uptake possible so that the greatest radiation dose may be delivered since too much delay in treating functional metastatic thyroid cancer may lead to progression of the disease. In addition, the advantage of increased uptake must be weighed against the radiation to the entire body which would be delivered from the radioactive iodine localized in a large amount of tumor.

When adequate uptake has been obtained, the optimal dose must be calculated. The adequacy of uptake is a function of the fractional uptake as well as of the mass of tumor to be destroyed. Arbitrary doses of 35 to 200 mc.<sup>88,89</sup> have been used. The uptake of radioiodine more accurately reflects tumor biochemistry than viability, in our experience, so that small doses of I-131 or external x-ray may cause loss of uptake without destruction of the tumor. For this reason we believe that for any given dose the maximum amount of radiation which can safely be administered should be given. In general, the limiting factor is blood radiation since the only fatalities after treatment with radioactive iodine have been due to pancytopenia. Even in non-fatal cases, bone marrow depression frequently is associated with isotopic irradiation. Thus there is a reasonably good correlation between lymphocyte depression and the blood dose of radiation after radioiodine administration.<sup>90</sup> It appears that a blood dose<sup>91,92</sup> of 500 rep is about the maximum that may be given safely in any one dose. This dose can be predicted from a study of the blood after a tracer dose in which the blood levels of radioiodine are determined for ten days to three weeks. In general there is agreement between the tracer and therapeutic doses except in those cases in which thyroglobulin is released into the blood stream,<sup>93-95</sup> in which instances the integral dose of radiation after a large amount may exceed the calculated radiation dose from the tracer study by a factor of 10. For this reason therapeutic doses which are smaller than that which might appear feasible from tracer studies are administered.

We have observed radiation pneumonitis and fibrosis in two patients with extensive pulmonary metastases from thyroid cancer after the administration of large doses of radioiodine. For this reason we have further limited our doses of radioiodine in patients with multiple small



pulmonary metastases so that 80 mc. or less of I-131 will localize in the lungs. This is an arbitrary figure since it is difficult to calculate the lung doses of radiation. With such a dose, however, no serious pulmonary fibrosis has been observed.

#### RESULTS AND COMPLICATIONS

From our observations<sup>87</sup> as well as those of others<sup>89,96-104</sup> it would appear that with some degree of selection more than half of the patients treated with radioactive iodine are benefited to some extent. Unfortunately, this form of therapy is not without its complications.

In addition to the pneumonitis and pulmonary fibrosis already mentioned, other less severe reactions have been noted. Radiation sickness, including nausea and vomiting, occur within the first day and the rapidity of onset is correlated with the dose and the rate of delivery,<sup>105</sup> while the severity is related to the whole body dose of radiation during the first eight hours.<sup>90</sup> A transient thyroiditis has been noted by ourselves and others.<sup>97</sup> In addition to the fall in lymphocytes<sup>90</sup> there may also be neutropenia and thrombocytopenia following large doses of total body radiation. The platelet fall usually does not occur until sometime after the lymphopenia.<sup>90</sup> Leukemia has occurred several years after treatment of cancer of the thyroid with radioactive iodine.<sup>87,106,107</sup> Amenorrhea has been observed after treating premenopausal women with large doses of radioactive iodine.<sup>72,77</sup> This has occasionally been permanent but pregnancy was possible in several patients who had received radioiodine in doses over 100 mc.<sup>72,108</sup> From a clinical standpoint hepatic damage has been minimal or absent but an elevation in bromsulfalein retention has been reported in a few patients after very large doses of I-131.<sup>72</sup> No renal damage has been reported.

The medical management of cancer of the thyroid gland with radioactive iodine can proceed rationally if account is taken of the physiologic forces which influence the distribution of the isotope. In view of the carcinogenic action of radioactive iodine on the thyroid glands of animals, one must be aware of this possible consequence of ionizing radiation in humans. In addition, the complications already noted clinically as well as the factors which determine radiation dosage also should be considered when this type of treatment is employed.

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# The Role of Radioactive Iodine in the Diagnosis of Thyroid Disease\*

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A LARGE number of procedures involving, at one step or another, the use of radioiodine are available for rather precise investigation of thyroid function. The purpose of this review is to analyze briefly the major known reactions that take place during the formation, release and degradation of the thyroid hormone and to suggest how these reactions may be measured. In nearly all cases the use of radioiodine is an important part of the determination and in many instances relatively simple procedures available in most isotope laboratories may be utilized for exact diagnoses. In particular, it is hoped that the fallacy of reliance on a single test for complete diagnosis of thyroid disease will be dispelled and the possibility of making a biochemical diagnosis suggested.

The accompanying tables list a few of the commonly used tests of thyroid function which employ radioiodine. Many modifications of these tests have been used but, in general, those listed in the table are relatively simple and give important data. The extrarenal disposal rate, the thyroid accumulation gradient and the four- or six-hour uptake are all useful tests. In a recent publication the relative efficiency of some of these tests in differentiating hypothyroidism and hyperthyroidism has been analyzed extensively.<sup>35</sup> Two of the tests listed are rarely performed for clinical diagnostic purposes (thyroid "organification" of iodine and thyroid secretion rate). The thyroid organification of iodine is included because it is easily evaluated by thiocyanate administration and may give important information not otherwise obtainable. The thyroid secretion rate, which may be determined in several ways, is listed because it represents the final function of the thyroid and is dependent upon all the steps preceding it. Many of the data listed in the tables are taken from

published studies. The ranges of values listed are not statistically evaluated since in most instances insufficient observations have been made to calculate these accurately or in some cases there is minor disagreement in published results. In many cases of the less common situations and tests only fragmentary results are available, or results are taken from studies designed to investigate other functions. The list of presenting situations might seem unduly long and complex, particularly in reference to previous treatment. These were included, however, because of the marked effect of drugs on the thyroid, which may persist for weeks. (Tables I to V.)

## IODIDE METABOLISM

The raw material which is both important for the formation of thyroid hormone and readily measurable is iodine. The thyroid gland appears to be limited in its ability to deal with iodine in any valence state other than as iodide. Fortunately, iodide and iodate appear to be the forms of iodine in most natural foods and water, and apparently the digestive tract can convert iodate to iodide. In most areas of the United States the level of iodide in the diet appears to be rather close to the minimum amount required. The iodine in the diet may be estimated from the amount of stable iodine appearing in the urine. In a group of eight normal persons living in the New York area and on an ordinary diet, the urinary iodine amounted to an average of 114  $\mu$ g. per day. This would correspond somewhat to a dietary intake of about 126  $\mu$ g. per day. As the normal amount of iodine secreted by the thyroid gland as a hormone is approximately 70  $\mu$ g. per day, this implies considerable efficiency of the thyroid gland in extracting iodine from the blood, in particular because the

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TABLE I  
VARIOUS PARAMETERS OF THYROID FUNCTION IN COMMON THYROID DISEASE

Diagnosis and Status	Thyroid Plasma I-131 Clearance (cc./min.)	Thyroid Organification of I-131	Thyroid Secretion Rate of Iodine ( $\mu$ g. I/day)	1-hour Uptake in Thyroid (%)	24-hour Uptake in Thyroid (%)	PBI-131 in Serum (%/L.)	Conversion Ratio
Euthyroid untreated	5-40 <sup>2,19,27,34,40,44</sup>	50 $\pm$ %/min. <sup>3,64</sup>	50-150 <sup>4,19,23</sup>	5-20 <sup>8,29</sup>	15-40 <sup>18,67</sup>	0.01-0.20 <sup>32,53,55,66,68</sup>	Less than 0.40 <sup>54</sup>
Hyperthyroid untreated	40-1,500 <sup>2,27,34,40,44</sup>	Normal	150-1,000 <sup>4,23</sup>	15-75 <sup>29</sup>	40-90 <sup>18,67</sup>	0.1-3.0 <sup>13,32,53,55,66</sup>	0.5-1.0 <sup>13,54</sup>
Hypothyroid primary untreated	0-4 <sup>2,34</sup>	?	Low <sup>4,23</sup>	Low	Low <sup>67</sup>	Depressed <sup>32</sup>	Less than 0.1 <sup>54</sup>
Hypothyroid panhypopituitarism	Low <sup>31,41</sup>	?	Low <sup>31,41</sup>	Low <sup>31</sup>	Low < 5% <sup>31,41</sup>	Low <sup>31</sup>	Less than 0.1 <sup>31</sup>

thyroid must compete with the kidney which in the normal human subject clears about 30 ml. of blood iodide per minute. The thyroid extracts iodide as such from the blood, and in animal experiments a convenient index of the ability of the thyroid to concentrate iodide is the T/S ratio which is the concentration of iodide in the thyroid relative to the concentration in serum one hour after the administration of I-131 and one and one-half hours after administration of an antithyroid compound such as thiouracil. This mechanism of concentration of iodide which is still not completely understood has been termed the thyroid trap for iodide. It seems reasonably clear that in the normal thyroid gland there is a vanishingly small quantity of iodide as such, and organification of iodine in the thyroid appears to be extremely rapid. The organification consists of the iodination of thyroglobulin, of which more will be mentioned later. Quite obviously, the thyroid trap depends upon more than some physical-chemical reaction in the thyroid for concentrating iodide. It depends upon the rate of blood flow to the thyroid gland. It must, furthermore, depend upon the rate of diffusion of iodide from the blood stream through the capillary wall, pericapillary tissue, through the thyroid cell and into colloid. Which is the slowest step, and hence the rate-limiting step in the normal human thyroid, is not clear at this time.

In the presence of a large amount of goitrogen\* thyroid activity after a single intravenous

\* A goitrogen is defined as any substance which can cause a goiter. There are at least two mechanisms, and

dose of I-131 increases for fifteen to sixty minutes and then falls at about the same rate as blood iodide. The rate of increase in thyroid activity (due allowance being made for extrathyroid loss of I-131) is a measure of thyroid blood flow and diffusion to the locus of trapping. The height of the peak is a measure of the concentrating mechanism if it is rapid, but varies in absolute quantity. Unfortunately, no data are available to delimit these functions precisely in any group of patients. It seems probable that similar plasma thyroid iodide clearances might be found despite variations in blood flow, diffusion or the iodide-concentrating mechanism. It seems likely that in some patients with hyperthyroidism blood flow determines the amount of iodide which is accumulated by the thyroid. Several excellent discussions of the problems presented by such considerations are available.<sup>5,69</sup> In general, perhaps the best way to measure the iodide trap and one which measures the net result of blood flow, diffusion and the concentrating mechanism, is the plasma iodide clearance. Measurement of the thyroid plasma iodide clearance is not particularly difficult and has been adequately described by several groups.<sup>2,4,27,34,40,44</sup> In most subjects accumulation of iodide by the thyroid

perhaps four, by which drugs may cause goiters through interfering with normal thyroid hormone formation. In the sense in which goitrogen is used herein the term refers to a drug which inhibits organification of iodine in the thyroid but does not prevent accumulation of iodide. Methimazole and thiouracil are the best known representatives of this group.

TABLE II  
EFFECT OF VARIOUS NON-THYROID DISEASES AND VARIOUS DRUGS ON CERTAIN PARAMETERS OF THYROID FUNCTION

Diagnosis and Status	Thyroid Plasma I-131 Clearance (cc./min.)	Thyroid Organification of I-131	Thyroid Secretion Rate of Iodine ( $\mu$ g. I/day)	1-hour Uptake in Thyroid (%)	24-hour Uptake in Thyroid (%)	PBI-131 in Serum (%/L.)	Conversion Ratio
Euthyroid, untreated	5-40 <sup>2,19,27,34,40,44</sup>	50 $\pm$ %/min <sup>3,64</sup>	50-150 <sup>4,19,23</sup>	5-20 <sup>8,29</sup>	15-40 <sup>18,67</sup>	.01-20 <sup>32,53,55,66,68</sup>	Less than 0.40 <sup>54</sup>
Euthyroid treated with anti,* off 2 days	5-100 <sup>+</sup>	50 $\pm$ %/min. <sup>3,64</sup>	Probably normal	May be elevated	May be elevated	May be elevated	May be elevated
Euthyroid treated with anti,* acutely	0-40 <sup>3,63</sup>	Close to zero <sup>63,65</sup>	Depressed	Usually depressed <sup>63</sup>	0-10 <sup>63</sup>	Low	Low
Euthyroid treated with thyroid	0-10	Normal	Probably depressed	Depressed	<20 <sup>14,56</sup>	Low	Probably low
Euthyroid treated with thyroid, off 3 weeks	5-100	Normal	Normal	May be elevated	May be elevated	Normal	Probably normal
Euthyroid, renal failure	2-20 <sup>34,42</sup>	Normal	Probably normal	Normal	May be normal or elevated <sup>42,56</sup>	May be normal	Low
Euthyroid, hepatic disease	May be increased	Normal	Probably normal	Probably elevated	20-80 <sup>39</sup>	?	?
Euthyroid, congestive heart failure	Normal	Normal	Probably normal	Probably normal	May be low or high <sup>11,26</sup>	Normal	Usually low <sup>54</sup>
Euthyroid, nephrosis	Probably elevated	Normal	?	Probably elevated	May be elevated <sup>43,56</sup>	Probably elevated	?
Euthyroid, low-iodine diet	May be elevated	Normal	Normal or depressed	May be elevated <sup>6</sup>	Elevated <sup>6</sup>	Probably elevated	Probably elevated
Euthyroid, cortisone or ACTH treatment	Decreased <sup>5</sup>	Normal	Normal	Probably decreased	Decreased <sup>20</sup>	?	?

\* Anti = a goitrogenic drug of the thiouracil type.

gland appears to be the rate-limiting step for thyroid hormone formation so that estimates of plasma iodide clearance provide a reliable index of the amount of thyroid hormone delivered per unit time, and hence an index of the patient's thyroid status. As already pointed out, the thyroid must compete with the kidney for iodine ingested in food and water, and, in general, because of much greater renal blood flow, more ingested iodine is lost in the urine than is accumulated by the thyroid. Therefore, indirect measurements of the iodine-concentrating mech-

anism of the thyroid, such as the one-hour uptake or the twenty-four-hour uptake, measure the net result of both thyroid and renal function. This becomes an important factor particularly in patients with renal disease. In the presence of renal disease the amount of iodine in the diet becomes particularly acute. If there is a generous iodine intake, the renal excretion may be so inadequate that the level of iodide in the blood rises markedly. When this happens, the fractional uptake by the thyroid may be decreased (that is, plasma thyroid iodide clearance falls) although



TABLE III

EFFECT OF VARIOUS TREATMENTS ON CERTAIN PARAMETERS OF THYROID FUNCTION IN HYPERTHYROIDISM

Diagnosis and Status	Thyroid Plasma I-131 Clearance (cc./min.)	Thyroid Organification of I-131	Thyroid Secretion Rate of Iodine ( $\mu$ g. I/day)	1-hour Uptake in Thyroid (%)	24-hour Uptake in Thyroid (%)	PBI-131 in Serum (%/L.)	Conversion Ratio
Hyperthyroid: Untreated	40-1,500 <sup>2, 27, 34, 40, 44</sup>	Normal	150-1,000 <sup>4, 23</sup>	15-75 <sup>29</sup>	40-90 <sup>18, 67</sup>	0.1-3.0 <sup>13, 32, 53, 55, 66</sup>	0.5-1.0 <sup>13, 54</sup>
Treated with anti* acutely	10-700 <sup>3</sup>	Depressed <sup>3, 64</sup>	150-1,000 <sup>4, 14</sup>	Elevated, normal or decreased	Decreased <sup>63</sup>	Decreased	Normal or decreased
Treated with anti,* off 2 days	40-1,500 <sup>3, 27</sup>	Normal <sup>64</sup>	Normal or decreased	Elevated	Elevated	Elevated	Elevated
Treated with iodine, off 2 wk.	Elevated <sup>26</sup>	Normal	Elevated	Elevated	40-90 <sup>26</sup>	Usually elevated	Elevated
Treated with iodine acutely	Depressed	Depressed <sup>62</sup> at least temporarily	Decreased to approximately normal <sup>12</sup>	Decreased	0-5 <sup>67</sup>	Depressed	Depressed
Treated with thyroid	Probably elevated	Probably normal	Elevated	Elevated	40-90 <sup>14</sup>	Probably elevated	Probably elevated
Euthyroid after I-131	Normal or elevated	Reduced <sup>23</sup> markedly	Probably normal	May be normal or elevated	Normal	May be elevated	May be elevated
Euthyroid postsurgery	Normal	Probably normal	Probably normal	Normal	Normal or elevated	May be high	May be high
Hypothyroid from surgery for hyperthyroidism	Low	?	Diminished	Low	May be low or normal	May be high <sup>7</sup>	May be high <sup>7</sup>
Toxic nodular goiter untreated	Usually elevated	Normal	Usually elevated	15-50	20-80 <sup>26</sup>	0.1-3.0 <sup>13</sup>	.01-1.0 <sup>13</sup>

\* Anti = a goitrogenic drug of the thiouracil type.

the total amount of stable iodine accumulated by the thyroid remains normal. The twenty-four-hour uptake may be normal or decreased because the lack of renal competition for I-131 permits continued accumulation. If, on the other hand, the iodine in the diet is low, the level of iodide in the blood may not rise very much. Under these conditions the plasma thyroid iodide clearance will be normal and the twenty-four-hour uptake elevated. In the absence of renal disease, iodine in the diet is also of considerable importance. The thyroid glands of patients living in areas in which there is a severe iodine

deficiency in the food and water may secrete entirely normal quantities of thyroid hormone but to achieve this end they develop hyperplastic thyroid glands and a markedly elevated thyroid plasma iodide clearance. This situation has been clearly described in a recent publication.<sup>10</sup> It seems reasonable to expect that persons on a moderately low-iodine diet might have moderately elevated thyroid plasma iodide clearances (or uptakes) and, at the other extreme, persons on a very generous iodine intake can be expected to have plasma iodide clearances below what we consider normal. In all these groups, the same

TABLE IV  
VALUES OF CERTAIN PARAMETERS OF THYROID FUNCTION IN VARIOUS THYROIDITIDES

Diagnosis and Status	Thyroid Plasma I-131 Clearance (cc./min.)	Thyroid Organification of I-131	Thyroid Secretion Rate of Iodine ( $\mu$ g. I/day)	1-hour Uptake in Thyroid (%)	24-hour Uptake in Thyroid (%)	PBI-131 in Serum (%/L.)	Conversion Ratio
Subacute thyroiditis, acute phase	Depressed <sup>33</sup>	?	Abnormal <sup>22</sup>	Probably low	0-20 <sup>33,67</sup>	?	Depressed
Subacute thyroiditis, subsiding	May be normal or elevated	Normal	Probably normal	May be elevated	May be normal or elevated	?	?
Hashimoto's disease	Normal <sup>33</sup>	?	May be low <sup>57</sup>	Usually normal	Normal <sup>33,67</sup>	?	?
Riedel's disease	Low <sup>33</sup>	?	Usually reduced	Probably normal	Normal <sup>33</sup>	?	?

TABLE V  
VALUES OF CERTAIN PARAMETERS OF THYROID FUNCTION IN PATIENTS WITH VARIOUS TYPES OF NON-TOXIC GOITER

Diagnosis and Status	Thyroid Plasma I-131 Clearance (cc./min.)	Thyroid Organification of I-131	Thyroid Secretion Rate of Iodine ( $\mu$ g. I/day)	1-hour Uptake in Thyroid (%)	24-hour Uptake in Thyroid (%)	PBI-131 in Serum (%/L.)	Conversion Ratio
Non-toxic nodular goiter, untreated	Usually normal	May be normal	Usually normal	5-15 <sup>29</sup>	10-60 <sup>26,67</sup>	Usually normal	Usually normal
Endemic goiter, untreated euthyroid	Probably high	Normal <sup>10</sup>	40-110 <sup>10</sup>	Usually elevated	50-70 <sup>10,26</sup>	Probably high	Probably high
Congenital goiter A, untreated	Presumably normal <sup>59</sup>	Absent <sup>36,37,59</sup>	Low <sup>59</sup>	May be elevated <sup>59</sup>	May be elevated <sup>59</sup>	Low or absent	Low
Congenital goiter B, untreated	Elevated <sup>60</sup>	Present but abnormal <sup>60</sup>	Elevated, $\pm 1$ <sup>60</sup>	Elevated <sup>60</sup>	90 $\pm$ 60	$\pm 0.4$	Elevated <sup>60</sup>
Congenital goiter C, untreated	High <sup>61</sup>	Present, abnormal <sup>21,37,61</sup>	Elevated <sup>61</sup>	Elevated <sup>61</sup>	90 $\pm$ 61	High <sup>61</sup>	High <sup>61</sup>

amount of stable iodine is concentrated in the thyroid glands. Both the acute and chronic effects of various diseases and drugs, on the thyroid plasma clearance of radioiodine are shown in the tables. Also the effects of various diseases which may affect certain parameters of thyroid function as measured with I-131 are also shown in the tables.

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Several technical problems should be noted at this point. The use of scintillation counters, with their high sensitivity, has greatly increased the possibility of studies with low levels of I-131 but at the same time has increased the problem of exact determination of thyroid uptake of I-131. The main problem is of back scattered radiation which increases the counting rate.

In a simple water phantom we found an increase of as much as 50 per cent in the counting rate, using an unfiltered 1 inch sodium iodide crystal. This 50 per cent increase refers to the counts made at identical distances of the same source of I-131 in water as opposed to its measurement in air. The use of a filter or of pulse-height discriminating circuits will, in general, resolve this problem. A filter will absorb the back scattered radiation because its energy is lower than that of the primary gamma ray. Similarly, the pulse-height discriminator will permit selective counting of any desired gamma ray energy and may be set to register only the primary gamma of iodine. A carefully constructed phantom neck may also be used to correct back scattered radiation. Another source of error is the misestimation or neglect of the contribution of I-131 in extrathyroid neck tissues to the total counts recorded by a counter centered over the thyroid gland. A few hours after administration of a tracer dose of I-131 this extrathyroid activity may comprise as much as 5 to 10 per cent of the dose.<sup>17</sup> This may be corrected by later tracers using overwhelming doses of NaI-127 (2 gm.) or by approximation methods. A tissue of about the same volume as the neck tissue may be used to correct the extrathyroid activity; counts over the thigh have been used for this purpose. After the iodide has been either excreted in the urine or accumulated by the thyroid, this factor is of almost negligible proportions.

#### INTRATHYROIDAL IODINE METABOLISM

Almost immediately upon entrance into the normal thyroid gland iodide is in some manner converted into an organic form, a step which is not readily reversible. Most probably this form is iodinated thyroglobulin. During the course of time, as increasing amounts of iodine are added to thyroglobulin, increasing amounts of monoiodotyrosine are formed, followed by elaboration of diiodotyrosine and finally of thyroxine. In the normal thyroid gland this process appears to proceed within the protein molecule. There is no firm evidence that the iodinated tyrosines are incorporated, as such, into the thyroglobulin molecule. Several discrete steps in this process and in the processes of proteolysis of thyroglobulin and deiodination of the tyrosines, all of which occur in the thyroid, will be subsequently described. Thyroid hormone is a term used to describe all the iodinated compounds secreted

into the blood. Thyroxine comprises at least 75 per cent and triiodothyronine 1 to 5 per cent of these compounds. Recently 3-3' diiodothyronine has been described in certain experimental animals but its role in human physiology remains to be elucidated.<sup>50</sup>

*Intrathyroidal Organification of Iodide.* The competence of this step is relatively easy to measure. The administration of 1 gm. of potassium thiocyanate or 100 mg. of perchlorate, either orally or intravenously, one hour after the administration of tracer quantities of I-131 will prevent further incorporation of radioactivity into the thyroid gland. In general, however, no acute fall in the amount of I-131 in the thyroid will be observed. Since thiocyanate or perchlorate will effectively wash out the iodide retained as such in the thyroid, this relatively simple test indicates the efficiency of the organification step. Several cases of goitrous cretins with a normal iodide trapping mechanism have been described but in these cases synthesis of thyroid hormone was blocked. Thiocyanate caused almost complete discharge of I-131 in the thyroid glands of these persons. In Table v this syndrome is called "congenital goiter A." Another interesting defect in thyroid organification of iodine has been described in subjects with hyperthyroidism treated with radioiodine. The relative values for several parameters of thyroid function in these cases may be seen in Table III. These persons may respond to thiocyanate administered an hour or two after a tracer quantity of I-131 with a fall of 10 to 50 per cent of the dose already accumulated in the thyroid. Apparently the radiation affects the processes involved in organification more strongly than it affects the iodide-concentrating mechanism. This defect is apparently of clinical importance since the thyroid plasma iodide clearance and the one- and four-hour uptake may be considerably elevated in the presence of secretion of the normal amount of thyroid hormone. In general the twenty-four- or forty-eight-hour uptake in these cases will fall within the normal range.

*Condensation of Iodotyrosines to Iodothyronines.* This would not appear to be a step that might be altered in diseased states since it has been demonstrated that diiodotyrosine in a tripeptide will spontaneously condense to form thyroxine. Nevertheless, a case has been described in which very careful chemical analysis of the thyroid gland removed at operation showed abundant quantities of iodinated tyrosines and



virtually no iodothyronines.\* In this situation, of course, thiocyanate will not discharge radioiodine accumulated in the thyroid and precise delineation of an error in metabolism occurring at this step is not simple. The use of excised thyroid tissue incubated with I-131 or the chemical analysis of excised thyroid tissue appears to be the only direct means so far available for the detection of this abnormality. In Table IV this defect is labelled "congenital goiter B."

*Synthesis of Thyroglobulin.* It might appear that a defect in the synthesis of this rather large (650,000 molecular weight) protein would not be rare, simply from a statistical standpoint. Nevertheless, no syndrome has been described so far which is characterized by an abnormal thyroglobulin.† Furthermore, a defect in the formation of thyroglobulin could easily lead to a defect in thyroid hormone synthesis. For example, certain proteins such as silk fibroin which contain what appear to be adequate amounts of tyrosine cannot be iodinated to form more than trace amounts of thyroxine. On the other hand, proteins such as casein and albumin may be readily iodinated *in vitro* to yield fairly substantial amounts of thyroxine. In fact, thyroglobulin is not a particularly favorable protein for iodination. In general, no more than 0.4 per cent thyroxine can be found in thyroglobulin whereas casein may be iodinated to form as much as 1.5 per cent thyroxine. It would therefore seem of some interest to explore the possibility that thyroglobulin may be abnormal in certain diseases of the thyroid. It is possible that the defect in thyroid hormone formation described as "congenital goiter B" represents, in fact, an abnormal thyroglobulin. A thyroglobulin with the tyrosine residues so arranged that condensation of any two is impossible from steric considerations is conceivable.

An interesting iodinated protein which may be found in the serum of certain patients with cancer of the thyroid has been described.<sup>47</sup> It appears to be about the same size as albumin (from ultracentrifuge sedimentation studies) and to release monoiodotyrosine and possibly thyroxine upon hydrolysis. This iodoprotein, termed compound X, may be an abnormal thyroglobulin or may represent a fragment of normal thyroglobulin. Unfortunately, studies on this

compound and on the structure of thyroglobulin require elaborate technics (salting out, chromatography, electrophoresis, ultracentrifugation). However, as paper electrophoresis becomes a routine laboratory procedure the electrophoretic mobility of I-131 labeled thyroglobulin may be determined to give at least some information on the charge state of this protein. It is a simple matter to incubate with I-131 200 mg. of sliced thyroid tissue removed at surgery and to examine the iodinated thyroglobulin formed.\*

*Proteolysis.* Thyroglobulin as such appears in the blood stream only when the thyroid gland is very heavily irradiated or otherwise damaged. Normally the proteolysis of this large protein molecule must be accomplished before the thyroid hormone can be delivered to the blood stream.<sup>48</sup> This is another step that could conceivably be altered in diseases of the thyroid but no examples of such an abnormality have yet been described. It is not, *a priori*, inconceivable that a defect in proteolysis of thyroglobulin could cause hypothyroidism and compensatory hyperplasia of the thyroid despite the presence of large amounts of iodine in the thyroid tissue. The effect of iodine in Graves' disease, which seems to be primarily a brake on the release of thyroxine by the thyroid, has been considered to represent such an inhibition of proteolysis. A real and abrupt decrease in thyroid secretion of thyroxine has been demonstrated as an effect of iodine in subjects with Graves' disease but the exact mechanism whereby this is achieved is not proved. The demonstration of an abnormality in proteolysis is rather complex and, as of this date, not feasible in ordinary clinical practice.

*Intrathyroidal Deiodination.* When thyroglobulin is hydrolyzed, not only the active thyroid hormone (thyroxine and triiodothyronine) but also iodotyrosines are released. Under ordinary circumstances iodotyrosines appear to be deiodinated and the iodine derived from these is then reutilized by the thyroid.<sup>52</sup> A defect in this mechanism could lead to the release of iodotyrosine in the blood stream. This possibility was investigated of recent date and was con-

\* Some of these procedures are well described in ref. 9, 38 and 49. It should be noted that some protein carrier should be added to thyroglobulin before it undergoes electrophoresis to prevent adsorption to paper. Human serum is a convenient mixture of proteins to use for this purpose. Normal human thyroglobulin has a mobility between the alpha-1 and alpha-2 globulins whereas compound X has a mobility identical with that of albumin.

\* See case 4 of ref. 60.

† An abnormal thyroglobulin was found in dogs chronically treated with thiouracil but it has not been completely characterized.<sup>51</sup>

clusively demonstrated in several cases of congenital goiter. (Table v.) These cases are referred to as "congenital goiter C" in Table v. The demonstration of this defect in thyroid hormone synthesis rests upon the demonstration of iodotyrosines in blood, which can probably be accomplished only by the chromatography of serum or extracts of serum after administration of I-131. A more direct way to demonstrate the absence of a deiodinase is direct demonstration of lack of deiodination of labeled diiodotyrosine by thyroid tissue.\* It should be noted that thyroxine, triiodothyronine and diiodotyrosine labeled with I-131 are available commercially.†

*Secretion Rate of Thyroid Hormone.* The rate of secretion of organic iodine by the thyroid gland reflects all the processes already described and should be a good measure of thyroid activity. Many ways have been proposed to measure more or less directly the rate of secretion of thyroid hormone iodine using I-131. In all instances measurements of the specific activity, usually of the protein-bound iodine in the blood, are necessary and in all cases serial measurements of thyroid, blood, urine and sometimes fecal radioactivity are required. Figures obtained by several authors using different methods are presented in the tables. These figures vary in euthyroid persons rather widely, from as little as 41  $\mu\text{g.}$  of thyroid hormone iodine per day<sup>23</sup> to as much as 175  $\mu\text{g.}$  per day.<sup>4</sup> Whether this marked variation is a result of difficulties in this measurement or represents biological variation is not clear. However, certain simplifying assumptions of most of the authors suggest that the former case is more likely. For example, in one instance, for purposes of calculation it was assumed that the specific activity of the blood organic iodine is equal to the specific activity of the thyroid organic iodine at some time after the administration of the tracer dose of I-131. This is in error, and its magnitude will vary as the rate of turnover of thyroid iodine varies. Another assumption made by other authors was that after the administration of labeled thyroxine the slowest rate of disappearance of radioactive iodine from the plasma represented the "degradation" rate of thyroxine. Depending upon the magnitude of the rate processes involved, this may represent a small or rather substantial error. In any event, these

measurements are important because they provide a more direct determination of the final phase of thyroid function, that is, the delivery of thyroid hormone into the blood stream. Thyroid hormone secretion rate calculated by any of the methods described by these authors does, in fact, correlate rather well with the clinical status of the patient, being markedly elevated in hyperthyroidism and depressed in hypothyroid states. It will be of interest to see if the existence of an unsteady state in the thyroid gland can be shown by these methods, with respect to iodine metabolism. Certainly an unsteady state must exist at some time during life, as the thyroid is able to accumulate as much as 200 days' supply of thyroid hormone. The reverse situation, what might be termed negative thyroid hormone balance, can be imagined to exist and might be delineated by these methods. Most methods of calculating thyroid hormone iodine secretion rate assume the presence of a steady state, so it is of importance to know how accurately this assumption is fulfilled. From a practical standpoint, it seems probable that with present methods a more reliable index of thyroid function is provided indirectly by measurement of some aspect of thyroid accumulation of radioiodine, as for example the plasma thyroid iodide clearance rate.

#### POST-THYROID IODINE METABOLISM

*Degradation of Thyroid Hormone.* The rate of degradation of thyroid hormone can be approximated with relative ease by measuring for fifteen to twenty days the amount of protein-bound I-131 in the blood after the administration of thyroxine labeled with I-131. Numerous such experiments have been described. Recently it has been suggested that patients with Graves' disease show an unusually rapid degradation of thyroxine;<sup>16,24</sup> earlier work seemed to suggest that the metabolism of thyroxine in Graves' disease was essentially normal.<sup>1</sup> Furthermore, Ingbar and Freinkel<sup>24</sup> demonstrated an abnormally rapid degradation rate of thyroxine in patients with Graves' disease who had been treated and at the time of study were in a euthyroid state. Were this the case, it would appear that cases of Graves' disease rendered myxedematous should require abnormally large amounts of desiccated thyroid hormone for the maintenance of the euthyroid state. So far this has not been described and does not appear to be the case. The possibility certainly

\* These same authors have also demonstrated that the cases of congenital goiter C lack a thyroid deiodase.<sup>58</sup>

† Abbott Laboratories, Oak Ridge, Tennessee.



remains, however, that there are clinical syndromes associated with an abnormally rapid rate of destruction of thyroid hormone.

*Excretion of Thyroid Hormone.* At present no states of thyroid disease exist which are definitely attributable to an increased or decreased rate of excretion of thyroid hormone. For many years it seemed likely that the low serum protein-bound iodine in subjects with nephrosis was a result of abnormally large loss of organic iodine in the urine of these patients. However, a recent study suggested that the urinary loss of organic iodine under these circumstances is inadequate to account for the lowering of protein-bound iodine seen.<sup>43</sup> From several studies, however, it does seem clear that certain abnormalities in thyroid function may occur in nephrosis. (Table II.) It still seems most likely that the increase in thyroid uptake of radioiodine and increased rate of release of thyroid radioiodine usually seen in nephrosis are a result of rapid degradation or excretion of thyroid hormone. Further studies are required to clarify this point. At this time no clear-cut cases of abnormalities in thyroid function resulting from an increased rate of excretion of thyroid hormone have been well documented.

*Alterations in the Thyroid Hormone-Protein Complex in Serum.* Thyroxine is bound rather firmly to what appears to be a specific alpha-globulin in serum. It seems likely that the firmness of the bond between thyroxine and protein is the cause of the rather slow rate at which thyroid hormone leaves the blood. The persistence of thyroxine in the blood after its intravenous administration is best demonstrated by comparison with the loss of adrenal cortical or gonadal hormones. Appreciable quantities of thyroxine may be demonstrated in the serum many days after its administration, whereas after the administration of hydrocortisone or testosterone vanishingly small quantities of the hormone may be found in serum three or four hours later.

There has been a suggestion that the thyroid hormone plasma protein complex is abnormal in patients with Graves' disease.<sup>15</sup> In particular, labeled thyroid hormone withdrawn from a patient with Graves' disease (previously given I-131 to label the thyroid hormone) disappears more rapidly when injected intravenously into a normal subject than does similarly labeled thyroid hormone from a euthyroid donor.<sup>16</sup> Very recently an increase in the amount of thyroxine-binding protein in the serum of pregnant women

has been described.<sup>45</sup> Whether this is primary to the elevation of protein-bound iodine seen in pregnancy is not clear. Also a case of binding of thyroxine by a gamma globulin observed in one subject with cancer of the thyroid has just recently been described.<sup>46</sup> Other abnormalities or differences in concentration of thyroxine-binding protein may perhaps be expected. The most direct method for investigation of the alpha-globulin which binds thyroxine is probably paper electrophoresis at pH 8.6 in which it can be shown that labeled thyroxine travels to a position intermediate between that of alpha-1 and alpha-2 globulin. Salting out and sedimentation in the ultracentrifuge of thyroxine-binding protein labeled with thyroxine I-131 have yielded further information about thyroxine-binding protein in normal subjects.

*Tissue Sensitivity to Thyroid Hormone.* Although many authors have speculated that tissue insensitivity to thyroid hormone may be responsible for some cases of clinical hypothyroidism, direct and convincing proof of this has not been readily forthcoming. By analogy with pseudohypoparathyroidism, in which tissue insensitivity to parathormone has been unequivocally demonstrated, there is the possibility of insensitivity to thyroid hormone. Recently a variant of tissue insensitivity has been suggested, namely, insensitivity to one of the thyroid hormones and not to the other. A series of patients with hypothyroidism did not improve appreciably upon therapy with thyroxine but made satisfactory improvement upon treatment with triiodothyronine.<sup>30</sup> Until the relationship between thyroxine and triiodothyronine is clarified it would seem premature to consider these cases of tissue insensitivity to thyroid hormone. It has been suggested that the only thyroid hormone active in tissues is triiodothyronine whereas thyroxine is effective only insofar as it is partially deiodinated in peripheral tissues to form triiodothyronine. If this hypothesis is correct the cases just mentioned might represent failure in the final step of thyroid hormone synthesis rather than any fundamental tissue failure to respond to the hormone. If so, it is somewhat surprising that more cases have not been described, because it lies within the province of any careful clinician to check the response of a patient to graded doses of thyroid. Measurement of oxygen consumption and serum cholesterol at frequent intervals can substantiate such a phenomenon. It was reported many years ago



that certain patients with mental disease, although not hypothyroid, did not respond to enormous doses of desiccated thyroid. Whether this represents failure of absorption, tissue insensitivity or alteration in some detoxifying mechanism is not clear. It should be noted that the response even to intravenous thyroxine is relatively slow and if equal doses of thyroxine are administered at daily intervals, the 95 per cent maximum response will not be seen for about two months. It is therefore important to be sure in all these studies that adequate time intervals are allowed.

#### IATROGENIC ABNORMALITIES IN THYROID FUNCTION

With the multiplicity of drugs now available to influence thyroid function, it is sometimes very difficult to distinguish in any individual case an inherent abnormality of thyroid function from changes in thyroid status induced by previous medication. The long-continued administration of antithyroid drugs may produce rather marked changes in thyroid function, as exemplified by the following cases.

**CASE I.** This patient, a thirty-five year old man, was referred for possible radiation thyroidectomy for intractable angina pectoris. The patient had been treated previously with propylthiouracil in dosages up to 2 gm. per day for a period of one and one-half years. At the time he was first seen he appeared to be in a clinically euthyroid state. However, he had a moderately enlarged thyroid gland, estimated to weigh about 40 gm., with an enlarged pyramidal lobe. The thyroid gland was soft and had a distinct bruit. The forty-eight-hour uptake of radioiodine was 70 per cent. No treatment was administered and the patient discontinued propylthiouracil. Tracer doses of radioiodine in the ensuing six months showed a gradual decline of uptake until approximately six months after stopping propylthiouracil, at which time the uptake was 30 per cent. By this time the patient's thyroid gland had decreased to normal size and the bruit had subsided.

*Comment:* Because of the clear-cut history of coronary insufficiency and the findings in this patient, a diagnosis of hyperthyroidism was never considered. Unfortunately, complete studies with radioiodine were not performed but it seems quite likely that this patient would have shown an elevated plasma thyroid iodine clearance, normal organification of iodine, an elevated conversion ratio and elevated protein-bound I-131. Had he been suspected of hyperthyroidism in the first instance, with suggestive clinical findings, the radioiodine uptake might have erroneously led to a diagnosis of hyperthyroidism.

**CASE II.** This patient was a thirty-eight year old man with Graves' disease recurrent after two thyroidectomies at the ages of seventeen and twenty-eight. Sensitivity to propylthiouracil with development of agranulocytosis occurred four years before he was admitted for study. In the last four years the patient had been taking about 100 mg. of iodine daily. When admitted he had classic Graves' disease with heat intolerance, nervousness and excessive appetite. He showed some proptosis and lid lag, hot sweaty skin and marked tremor of the hands. His thyroid gland was very firm and irregularly enlarged to an estimated weight of 70 gm. The basal metabolic rate was +76 per cent, the protein-bound iodine 18  $\gamma$  per cent and a tracer dose of I-131 showed 70 per cent uptake in forty-eight hours. However, daily measurements of serum protein-bound I-131 showed levels never exceeding 0.20 per cent/L., a figure sometimes found in euthyroid individuals. The half-life of I-131 in his thyroid when recirculation was prevented with thiocyanate was about twenty days. From data on protein-bound I-127 in serum and multiple thyroid readings it was possible to calculate that the iodine in this patient's thyroid gland amounted to 28 mg.

*Comment:* The extraordinarily large store of stable iodine in his thyroid gland seems due to prolonged treatment with Lugol's solution, resulting in a low protein-bound I-131, a slow thyroid loss of I-131 and, upon treatment with I-131, a prolonged period before a euthyroid state developed.

**CASE III.** This patient, a thirty-five year old woman, gave a history of classic Graves' disease developing six years previously; this had responded well to subtotal thyroidectomy. Four years previously acromegaly developed which appeared to be controlled by 2 million volt x-ray therapy to the pituitary. One year prior to admission recurrence of goiter developed as well as symptoms of hyperthyroidism, which progressed until hospital admission. At this time the patient exhibited the characteristic appearance of acromegaly, plus the typical findings of severe hyperthyroidism. The thyroid gland was soft and was estimated to weigh 125 gm. The basal metabolic rate was +45 per cent and a tracer dose of I-131 showed 31 per cent in the thyroid at forty-eight hours. The urinary excretion was 17 per cent on the first day and 3 per cent on the second. Her serum protein-bound I-131 reached 3.1 per cent/L. Thiocyanate was administered from two days after the tracer dose for fourteen days; her thyroid uptake fell at a half-life of two days. After two weeks of thiocyanate her serum protein-bound iodine fell from 9.5  $\gamma$  per cent to 4.5  $\gamma$  per cent and a euthyroid state developed. It was calculated that she had approximately 0.4 mg. of iodine in her thyroid gland.

*Comment:* The fact that the goiter was recurrent after surgery probably accounted for the unusually small amount of iodine in the thyroid gland. This fact, in turn, led to the relatively low forty-eight-hour uptake,

very rapid thyroid release rate and unusually high serum protein-bound I-131.

#### CLINICAL DIAGNOSIS OF THYROID DISEASE

In the preceding discussion it has been tacitly assumed that complex and difficult tests of thyroid function, particularly those employing radioactive iodine, are not only necessary but are also desirable for establishing the diagnosis of thyroid disease. This is true only in part. While it is certainly evident that very careful biochemical diagnosis and the description of new syndromes of thyroid dysfunction require many or most of the tests mentioned, diagnosis of the average patient suspected of having thyroid disease does not depend on elaborate function tests. Careful clinical judgment is still of paramount importance in diagnosis. A detailed history, meticulous examination and a certain degree of clinical acumen serve as the foundation for the diagnosis of thyroid disease. In particular, repeated observation of the patient over a period of weeks or months frequently serves to confirm or exclude possible diagnoses. A further procedure of which little is written these days is the therapeutic trial. In patients suspected of hyperthyroidism a course of treatment with iodine and frequent estimations of serum cholesterol and oxygen consumption, plus careful observation, will usually serve to establish or rule out a diagnosis of hyperthyroidism when most of the complicated laboratory procedures are equivocal or contradictory. Normal subjects given iodine in a dose of 50 mg. or so per day will almost never show a rise in serum cholesterol and fall in the basal metabolism in the course of a few weeks. Patients with hyperthyroidism, and particularly those with Graves' disease, almost always show both a rise in cholesterol levels and a fall in the basal metabolic rate within two weeks of initiation of therapy with iodine. The use of desiccated thyroid or triiodothyronine and I-131 uptake to differentiate hyperthyroidism from euthyroidism has been described and the results of such procedures are seen in the tables. The use of thyroid-stimulating hormone has also been proposed to diagnose cases of minimal or potential hypothyroidism.<sup>25</sup> Certain patients with just barely adequate thyroid function may fail to show an increased uptake of I-131 after thyroid-stimulating hormone administration. This same lack of response to thyroid-stimulating hormone has been found also in almost all cases of Hashimoto's struma.<sup>57</sup>

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The use of I-131 for anatomic localization of thyroid tissue may frequently be helpful. Struma ovarii, lingual thyroids, substernal thyroids and occasional cancers of the thyroid may be diagnosed in this way.

Radioactive iodine should be administered with discretion. It is impossible to administer radioiodine without delivering radiation to the thyroid gland. Even now with sensitive detectors and reduced doses of radioiodine it is easy to forget that a 10  $\mu$ c. tracer in a normal individual will deliver approximately 15 rep to the thyroid gland. This represents the amount of radiation that would normally be permitted as "the maximum permissible safe dose" throughout the course of an entire year. Larger doses of radioiodine may frequently be necessary for some of the more detailed procedures previously outlined in this paper and the radiation delivered to the thyroid will be proportionately greater. It should be borne in mind, therefore, that the administration of any tracer dose of radioiodine represents a calculated risk. It is a risk that is entirely justified if the information gained has a good chance of benefiting the patient. Radioiodine tracers to children especially should be viewed with considerable caution. The ease of administration of radioiodine and the lack of any acute effects of even large doses cannot help but encourage carelessness. Recently use of I-132 which has a half-life of 2.3 hours and will therefore deliver for any given dose substantially less thyroid radiation, has been proposed.<sup>17</sup> For certain tests of thyroid function, such as plasma thyroid iodide clearance or the one-hour thyroid uptake, this isotope has considerable promise. These data may be easily secured and the radiation to the thyroid may be reduced by a factor of as much as thirty. Routine use of this isotope for certain diagnostic tests of thyroid function consequently will diminish the danger of radiation damage.

#### SUMMARY

The major pathways of thyroid hormone formation and metabolism are described.

Tests which determine the rate or examine the competency of most of these steps are described. Careful application of appropriate tests will serve to establish a biochemical diagnosis of thyroid disease in most individuals. Clinical judgment, however, remains the final factor in establishment of a diagnosis.

The inevitability of radiation to the thyroid



when using radioiodine is emphasized and the need for caution in its use is stressed.

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# Physiology and Treatment of Myxedema\*

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IN 1874 Gull<sup>1</sup> presented graphically the clinical features of thyroid deficiency in adults. Four years later Ord<sup>2</sup> cited instances of atrophy or fibrosis of the thyroid gland observed at autopsy in patients who had had the disease, and he coined the descriptive, diagnostic term "myxoedema." Since these early observations little has been added to the clinical description of myxedema but much knowledge has evolved concerning the physiologic and pathologic alterations in the body which result from deficiency of the thyroid hormone.

The history of the treatment of myxedema is of interest, for replacement therapy with thyroid represents the first successful treatment of endocrine deficiency.<sup>3</sup> Crude extracts of thyroid gland were first employed. Later, desiccated thyroid gland in pulvules or tablets was found wholly effective when given orally, and today this is the most widely used and least expensive agent for the treatment of myxedema.

## NATURE AND ACTION OF THE HORMONE

The exact identity of the thyroid hormone is not yet known. Thyroxine, readily isolated from the thyroid gland,<sup>4</sup> assuredly is important, for it has been identified in plasma<sup>5,6</sup> and on administration to athyreotic subjects the manifestations of thyroid deficiency are corrected. Recently, however, triiodothyronine has been found in small amounts in the thyroid gland;<sup>7</sup> it occurs in minute quantities in blood<sup>8</sup> and has been found in slightly greater amounts in blood taken from the thyroid vein.<sup>9</sup> Since this compound has a more rapid metabolic effect than thyroxine in myxedema,<sup>10,11</sup> as well as greater potency,<sup>12</sup> it also appears to have significance.

The manner and site of action of the thyroid hormone are at present receiving intensive study. Abundant evidence exists that administration

of thyroxine or triiodothyronine to a normal or thyroid-deficient animal accelerates oxygen utilization,<sup>13</sup> and that tissues isolated from such an animal use more oxygen *in vitro* than tissues from an untreated animal.<sup>14,15</sup> On the other hand, it has never been demonstrated conclusively that the addition of thyroxine or triiodothyronine to a medium containing intact tissues *in vitro* from normal or myxedematous animals has any stimulatory effect on the oxygen consumption of such tissues.<sup>14,15</sup> Under certain experimental conditions, however, the addition *in vitro* of thyroxine or triiodothyronine to homogenates or mitochondria prepared from tissues of normal animals induces an immediate increase in oxygen utilization of such preparations.<sup>15-17</sup> Furthermore, thyroxine uncouples oxidative phosphorylation in these systems<sup>17-20</sup> and it has been postulated that this is an essential action of the thyroid hormone. Certain other compounds also perform this latter function,<sup>21-24</sup> although they do not correct myxedema; so it may be that there are other specific effects of the thyroid hormone not yet defined.

## PHYSIOLOGY

Upon removal of the thyroid gland or upon failure of the gland to elaborate its hormone (or hormones) profound metabolic alterations occur. These changes develop slowly, often insidiously, and, although they can be detected shortly after loss of the hormone, several months are usually required before the manifestations of myxedema are marked. (Fig. 1.) Myxedema is often conspicuous in children since it is accompanied by an associated failure of growth. (Fig. 2.)

It is important to recall that the thyroid hormone only accelerates metabolic processes and that with lack of the hormone body functions

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FIG. 1. Spontaneous idiopathic myxedema (Gull's disease) in a seventy-one year old widow. Symptoms of fatigue and weakness for fifteen years, puffiness beneath eyes for ten years, intolerance to cold, hoarse voice, dry coarse skin, poor appetite and chronic constipation for five years. Note the periorbital edema, coarse skin and dull expression. The ecchymotic area under the right eye resulted from a fall precipitated by dizziness and weakness. During replacement therapy there was subjective and objective improvement, but doses of desiccated thyroid greater than 32 mg. daily could not be tolerated because of development of anginal pain.

continue at a reduced rate. Accordingly, a state of thyroid deficiency is not usually of itself fatal, but may lead to early demise of the patient from other causes.

**Body Fluids.** In myxedema, body weight is usually increased due in large measure to the retention of water in the tissues. In long standing myxedema with inanition, body weight may, of course, be decreased despite the presence of excess fluid. This retained fluid is chiefly contained in the extracellular space, as suggested by measurements of this space with thiocyanate<sup>25</sup> and radiosodium.<sup>26</sup> Although the content of exchangeable sodium in the body is high in myxedema, the concentrations of sodium, potassium and chloride in the serum may not deviate



FIG. 2. A, untreated cretin at age six years and two months. The height of the child was that of an average healthy child of two and one-half years. The bone age by x-ray study was six months. The child was apathetic; the skin cool and pallid. Note infantile naso-orbital configuration and protuberant abdomen. No goiter was observed. Thyroidal accumulation of radioiodine was slight and insignificant. B, same patient seven and one-half years of age, after treatment with desiccated thyroid, 128 mg. daily, for sixteen months. The patient had grown approximately  $7\frac{1}{2}$  inches attaining height of an average healthy child of five and one-quarter years. Bone age five years. Marked improvement in development, definite improvement in mentation. (History and photographs kindly supplied by Dr. Lawson Wilkins.)

significantly from normal.<sup>25,26</sup> These alterations in body fluids and electrolytes may in part be due to increased capillary permeability.<sup>27</sup> On institution of therapy with desiccated thyroid there is a further transient expansion of the extracellular fluid volume followed by a diuresis of water, sodium and chloride, along with a decrease in body weight.<sup>28</sup> Since myxedema fluid contains excess protein, a marked diuresis of nitrogen and phosphorus also occurs on initiation of treatment.<sup>29</sup>

**Protein Metabolism.** Specific alterations in nitrogen and protein metabolism in myxedema



have been delineated in recent studies. The serum may contain less albumin and gamma globulin than normal; on the other hand, beta globulin and total protein may be increased.<sup>30</sup> Serum mucoproteins have been variously reported as excessive<sup>31</sup> or diminished.<sup>32</sup> The protein content of cerebrospinal fluid is increased.<sup>33</sup> The concentrations in tissues of numerous enzymes (themselves proteins) are diminished.<sup>34-36</sup> The significance of these observations is not entirely understood.

In animals nitrogen excretion increases following thyroidectomy,<sup>37,38</sup> and the rate of amino acid catabolism is accelerated.<sup>39</sup> In patients with myxedema synthesis of protein is impaired;<sup>40</sup> this probably accounts in large measure for the failure of the thyroid-deficient young animal<sup>41</sup> or child<sup>42</sup> to show proper growth. Moreover, thyroid hormone is essential for maturation of skeletal epiphyseal centers<sup>43</sup> which in hypothyroid children show altered development and delayed closure.<sup>44,45</sup> (Fig. 3.)

**Carbohydrate Metabolism.** Carbohydrate metabolism is not markedly altered in myxedema. The rate of absorption of glucose from the intestine may be reduced,<sup>46</sup> and carbohydrate tolerance may be slightly increased.<sup>47</sup> Thyroidectomy prior to pancreatectomy in rats prevents the development of diabetes, and the development of hypothyroidism in man may be associated with amelioration of existent diabetes.<sup>48</sup>

**Cholesterol Metabolism.** Elevation of the concentration of serum cholesterol is well recognized in patients with myxedema;<sup>49</sup> serum levels of cholesterol esters, phospholipids and total fatty acids, as well as of free cholesterol, are increased.<sup>50-52</sup> These changes, however, may represent only a shift of cholesterol from tissues to plasma since total body cholesterol content remains constant.<sup>53</sup> More recent studies employing tritium have revealed decreased synthesis of cholesterol by the liver but this is associated with marked decreases in rates of destruction and biliary excretion of cholesterol.<sup>54</sup> These results appear to offer some explanation for the occurrence of hypercholesterolemia in myxedema.

**Creatine.** The amounts of creatine in serum and urine are diminished in myxedema,<sup>55</sup> creatine tolerance is increased,<sup>56</sup> and the conversion of creatine to creatinine is stated to be augmented.<sup>57</sup> On initiation of therapy with desiccated thyroid a temporary rise in urinary excretion of creatine and creatinine occurs.<sup>58</sup> Creatinuria probably represents loss of stored

creatine from the muscles,<sup>57,58</sup> together with improved renal function.

**Vitamins.** It is well established that in the presence of deficiency of the thyroid hormone the conversion of carotene to vitamin A is impaired;<sup>59,60</sup> this accounts for the carotinemia which is occasionally observed in patients with myxedema.<sup>61</sup> On diets devoid of vitamin A, thyroidectomized animals fed carotene develop vitamin A deficiency, whereas no deficiency occurs in thyroid-intact animals given carotene.<sup>59</sup> No evidence of disturbed functions of the B complex vitamins in myxedema has appeared. The occurrence of pernicious anemia in hypothyroid patients is not unusual, and in such patients there is, of course, a deficiency of vitamin B<sub>12</sub>.<sup>62</sup>

**Adrenal Function.** The effect of thyroid deficiency upon the functions of the other endocrine glands has recently received much attention. In animals receiving thiouracil or in thyroidectomized animals, atrophy of the adrenal cortices occurs<sup>63-65</sup> but the response of such atrophic adrenals to adrenocorticotrophic hormone (ACTH) is apparently normal.<sup>66</sup>

The ability of the myxedematous patient to excrete an increased water load is impaired in primary myxedema, as in primary adrenal insufficiency; this abnormality in myxedema is unaltered by cortisone but is corrected by desiccated thyroid.<sup>67</sup> Furthermore, in patients with myxedema urinary excretion of 17-ketosteroids is markedly decreased below the normal range.<sup>68-72</sup> It is stated that excretion of 17-ketosteroids returns to normal after replacement therapy with thyroid;<sup>72</sup> an observation to the contrary has also been reported.<sup>69</sup> Urinary corticosteroid and 17-hydroxycorticosteroid excretions are also low<sup>73,74</sup> but plasma levels of 17-hydroxycorticosteroids may be normal due to the diminished rate of removal by the tissues.<sup>74</sup> In hypothyroidism the adrenal cortex of man, like that of animals, responds to exogenously administered ACTH;<sup>75-77</sup> this suggests that in myxedema the secretion of ACTH is depressed, or the adrenal responds only to excess ACTH stimulation, or both.

These observations on altered adrenal function in myxedema emphasize the difficulties occasionally encountered in the clinical differentiation of adrenal cortical insufficiency due to myxedema from that due to primary adrenal or pituitary disease.<sup>78</sup>

**Gonadal Function.** Menstrual irregularities, usually excess flow, infertility and failure to



FIG. 3A. Epiphyseal dysgenesis in newborn, hypothyroid infant. The mother of the infant received propylthiouracil for thyrotoxicosis during pregnancy. The initial dose, 300 mg. daily, was continued at this level even after euthyroidism was achieved and was, therefore, probably excessive. Note the indistinct and scattered foci of ossification in the epiphyses, as has been described by Wilkins<sup>42</sup> and others in cretinism. The mother was not allowed to nurse the child. Six weeks later x-ray examinations showed normal epiphyseal development. The infant's growth and development have been normal.

show evidence of ovulation are commonly noted in hypothyroid women.<sup>79</sup> However, pregnancy occurring in myxedematous women is not unknown.<sup>80,81</sup> Diminished libido and potentia occur in men with myxedema. The fertility of hypothyroid animals is usually diminished.<sup>82</sup>



FIG. 3B. Normal epiphyses in newborn. The mother of this infant also received propylthiouracil for thyrotoxicosis during pregnancy. Overdosage was avoided. The centers of ossification in the epiphyses are clearly developed.

In athyreotic female rabbits ovulation does not occur and graafian follicles persist without appearance of corpora lutea.<sup>83</sup>

It has been suggested that deficiency of thyroid hormone impairs the release or production of gonadotropic hormones.<sup>84</sup> This is consistent with the finding that myxedematous postmenopausal women have decreased urinary excretion of follicle-stimulating hormone.<sup>69,72</sup> On the other hand, in men and premenopausal women with myxedema a normal excretion

occurs in some patients and a diminished excretion in others.<sup>69,72</sup>

**Cardiovascular Function.** Deficiency of the thyroid hormone results in significant alterations in the function of the cardiovascular system.

The heart may be dilated, although this does not usually occur without concomitant hypertension or congestive heart failure.<sup>85</sup> Bradycardia, low cardiac output and low voltage in the electrocardiogram are common and may be due to pericardial effusion which probably occurs more often in myxedema than is generally recognized.<sup>86-88</sup>

Whether or not myxedema with hypercholesterolemia accelerates the development of atherosclerosis has not been settled. A recent study<sup>89</sup> indicates that the incidence of coronary atherosclerosis in patients with myxedema is not greater than in euthyroid persons; this is contrary to views held previously.

**Miscellaneous Changes.** Other observations of derangement of function in myxedema which are of interest have been noted. Slight degrees of proteinuria are common; studies of renal function reveal a depression of glomerular filtration rate, renal plasma flow,  $Tm_{PAH}$  values and urea clearance, but concentrating power is normal.<sup>90-93</sup>

Anemia is usually present. Although various alterations in the size and hemoglobin content of red blood cells occur in different patients, hypochromic, macrocytic anemia is more frequently noted.<sup>94,95</sup> These abnormalities have been explained in part by hypoplasia of the cellular elements of the bone marrow, which is edematous.<sup>95</sup> Gastric hypochlorhydria or achlorhydria often exists,<sup>96,97</sup> perhaps contributing to digestive symptoms in some patients. The colon may be dilated,<sup>98</sup> contributing to constipation.

Reduction in cerebral blood flow with increased vascular resistance and diminished cerebral consumption of oxygen and glucose may be responsible for mental changes and poor memory.<sup>99</sup> Electroencephalograms reveal low voltage and slow frequency.<sup>100</sup> Retardation of the relaxation of the deep tendon reflex responses is due to an abnormal contractile mechanism of the muscle rather than to altered function of peripheral nerves;<sup>101,102</sup> moreover this may account for the generalized hypotonicity and weakness of the muscles which is often observed.

Various levels of magnesium in serum have been reported to occur in myxedema.<sup>103,104</sup> Urinary excretion of magnesium increases after

administration of triiodothyronine to a patient with myxedema.<sup>105</sup>

#### ETIOLOGIC FACTORS

The causes of thyroid hormone deficiency may be generally classified as follows: (1) loss of the thyroid gland by spontaneous atrophy, ablation or involvement by disease process, (2) failure of the pituitary to elaborate thyroid-stimulating hormone, (3) decrease in thyroid hormone production by chemical means as may occur in severe iodine deficiency or by ingestion of goitrogenic foods or drugs, and (4) inborn errors in thyroidal synthesis of hormone.

**Atrophy and Ablation.** In adults, as well as in children, spontaneous idiopathic atrophy of the thyroid may occur. The mechanism of the thyroid loss is not clear in all instances. As Ord<sup>2</sup> described, the gland becomes atrophied, becoming only a strand of fibrous tissue. In some patients atrophy may be due to the unique failure of the pituitary to elaborate thyrotropic hormone while continuing to produce its other hormones in a normal and adequate manner;<sup>106,107</sup> this condition can usually be established by investigative methods which show no loss of other tropic pituitary hormones and which establish that thyroid function is accelerated by administration of exogenous thyrotropic hormone.

In infants, congenital dysgenesis or agenesis of the thyroid may exist;<sup>108</sup> this is known as sporadic cretinism. Cretinism may also appear endemically as a result of iodine deficiency.

Ablation of the thyroid may result from surgery, radioiodine or, more rarely, from external x-ray radiation. It is of interest that purposeful, presumed total thyroidectomy may not result in myxedema and conversely that myxedema occasionally follows subtotal thyroidectomy. In hyperthyroid patients who have undergone apparent total thyroidectomy, remnants of thyroid tissue remaining in the neck may become sufficiently hypertrophied to prevent thyroid deficiency.<sup>109,110</sup> On the other hand, approximately 3 per cent of patients undergoing subtotal thyroidectomy for Graves' disease later develop myxedema;<sup>111</sup> in such instances it must be assumed that the remnant of thyroid tissue remaining at the conclusion of the operation probably loses viability either from surgical interference with the blood supply or as a result of pressure necrosis from hemorrhage into the neck tissues.

The incidence of hypothyroidism following



radioiodine therapy of hyperthyroidism is about 3 to 8 per cent.<sup>112,113</sup> In patients with normal thyroid function myxedema can usually be induced by administration of about 30 mc. of radioiodine;<sup>114</sup> there is, however, much variation in the amount required.

Diseases giving rise to goiter and concomitant myxedema are uncommon. When such occur, Hashimoto's struma is usually the cause.<sup>115</sup>

An infrequent cause of myxedema is atrophy of the thyroid gland following subacute thyroiditis.<sup>116</sup> Carcinoma of the thyroid rarely produces myxedema; the tumor usually spreads beyond the capsule of the gland rather than remaining invasive within the gland.

*Absence of Thyrotropic Hormone.* Myxedema due to this cause is known as "secondary" or "pituitary myxedema." In addition to the unique loss of thyrotropic hormone, already described, the pituitary may fail entirely when it becomes involved by atrophy or disease. Post-partum necrosis of the pituitary, involvement of the pituitary by tumor (such as chromophobe adenoma) or by sarcoid, tuberculosis, histoplasmosis, and the like, are the more usual causes of destruction.<sup>117</sup> Of course, surgical removal of hypophysis also results in thyroid deficiency.<sup>118</sup>

*Hormone Insufficiency by Chemical Means.* Severe iodine deficiency can, of course, give rise to goiter and hypothyroidism but this is now most uncommon in this country; indeed, overt myxedema was but rarely observed in the study of edemic goiter by Stanbury and his associates<sup>119</sup> in Mendoza, an iodine-deficient province in Argentina.

Certain goitrogenic foodstuffs, such as cabbage and rutabaga, also may produce goiter and rarely hypothyroidism by preventing thyroid accumulation of iodide.<sup>120</sup> This is unlikely to occur, however, unless the diet consists entirely of goitrogenic food or if the diet is low in iodine content. Administration of thiocyanate,<sup>121</sup> para-aminosalicylic acid<sup>122</sup> or resorcinol<sup>123</sup> and, theoretically, perchlorate, like the goitrogenic foodstuffs, may produce hypothyroidism; this can be prevented by administration of iodide. It is important to recognize that withdrawal of the goitrogenic substance and immediate introduction of iodide therapy may be followed by such a rapid uptake of iodide by the gland and production and elaboration of hormone that brisk hyperthyroidism may ensue. This method of inducing hyperthyroidism in animals was first reported by Webster and Chesney,<sup>124</sup> and is

similar to "Jod-Basedow's disease" in man.<sup>119,125</sup>

It has been suggested recently that cobalt may induce goiter;<sup>126,127</sup> in some instances hypothyroidism also results.<sup>128</sup> Of unusual interest are the recent reports that in man administration of iodide in excess may occasionally induce goiter and hypothyroidism.<sup>129,130</sup> The mechanism of this curious phenomenon is unknown but it may be an inhibition of organic binding of iodine in the gland which results in diminished synthesis of hormone.<sup>131</sup>

*Inborn Errors in Hormone Synthesis.* Goitrous cretinism has been frequently described in recent years.<sup>132-134</sup> In these patients there is no iodine deficiency to account for failure of the gland to synthesize adequate hormone. The hyperplastic gland takes up iodide excessively, and in some patients the organic binding of iodine is impeded, whereas in others abnormal compounds are formed which have ineffectual calorogenic properties.<sup>135</sup> Administration of desiccated thyroid, of course, relieves myxedema.

More recently it has been pointed out that some nodular goiters in adults may be akin to the phenomenon described in goitrous cretins and children.<sup>136</sup> The goiter shows areas of marked hyperplasia. Overt myxedema is not described.

#### LABORATORY AIDS IN DIAGNOSIS

In recent years improved and exacting methods have become generally available to assess thyroid function. The basal metabolic rate, long a standard procedure, has been modified by Bartels,<sup>137</sup> who achieves increased accuracy of the procedure by subjecting the patient to light barbiturate anesthesia during the test, thus determining the somnolent metabolic rate.<sup>138</sup> The method requires the care attendant upon induction of and recovery from anesthesia. Other improved methods of determining metabolic rate are much needed clinically since, as will be mentioned, some laboratory tests recently devised are not satisfactory if the patient has received iodide, an antithyroid drug or mercurial diuretic.

The level of serum cholesterol remains an important adjunct in diagnosis. In primary myxedema the level is usually elevated, whereas in myxedema secondary to pituitary insufficiency the serum cholesterol may be within normal limits.<sup>139</sup> Exceptions to this generalization have been noted.<sup>140,141</sup> Towery<sup>142</sup> observed low levels of serum cholesterol in a patient with primary myxedema during severe starvation; during a

period of good intake of food prior to thyroid replacement therapy the patient developed markedly elevated levels of cholesterol in the serum.

Since thyroxine is carried in the blood attached to protein,<sup>143</sup> chemical assay of the quantity of iodine bound to protein reflects the quantity of circulating thyroid hormone. In normal subjects the level of protein-bound iodine varies from about 3.5 to 8.0  $\mu\text{g}$ . per 100 ml. serum. In overt myxedema the level may be between 0 and 2.5 and is usually about 0.5  $\mu\text{g}$ . per 100 ml. serum. A small quantity of non-hormonal protein-bound iodine (about 0.25 to 1.0  $\mu\text{g}$ . per 100 ml. serum) is present; this moiety is markedly increased if excess iodine is ingested and, in such instances, to be sure, the serum protein-bound iodine level is of no diagnostic value. The method of determination of the butanol-extractable iodine, as developed by Man and her associates,<sup>144</sup> eliminates non-hormonal iodine, the resultant value representing more clearly thyroxine-iodine. Mercurial diuretics adversely alter the determination of the serum protein-bound iodine; the spurious result is low.<sup>145</sup>

Finally, establishment of the diagnosis of myxedema has been much aided by the use of tracer quantities of radioiodine. Such tests are based on the avidity of the gland for iodine and measure the rate of accumulation and turnover of radioiodine by the thyroid gland. Methods are numerous and include (1) direct measurement of radioiodine uptake by the thyroid gland, (2) measurement of urinary radioiodine excretion, (3) measurement of the neck-thigh ratio of radioactivity, and (4) measurement of the rate at which radioiodine appears in the serum protein-bound iodine fraction. Excess iodine administration interferes with these tests.

Radioiodine tracer tests and serum protein-bound iodine determinations have facilitated the differentiation of secondary from primary myxedema. In patients with secondary myxedema the administration of thyrotropic hormone results in increased accumulation of radioiodine by the thyroid and a rise in the level of serum protein-bound iodine; in patients with primary myxedema no effect is observed.<sup>146-148</sup>

#### NATURAL COURSE OF UNTREATED MYXEDEMA

Little is published on the natural course of untreated myxedema since, fortunately, the

disease is usually recognized and treated. There are, however, classic observations on untreated myxedema, a unique publication being that of the London Myxoedema Commission<sup>149</sup> in 1888. Death in patients with myxedema is usually attributable to intercurrent infection, heart failure or debilitation. Fatal coma in patients with myxedema is also recorded.<sup>150</sup> Mortality rates of patients with either treated or untreated myxedema have not been determined; a study in 1951 by the Association of Actuaries indicates that mortality rates of hypothyroid subjects are somewhat increased over the average rates but the diagnosis of hypothyroidism was not clearly established in all subjects.<sup>151</sup>

The occurrence of psychotic states, which Asher has so aptly termed "myxoedematous madness,"<sup>152</sup> may occur more often than is generally appreciated, and incarceration of patients in mental institutions for many years has been known to occur. In such patients the psychotic state usually is relieved by thyroid therapy.

#### TREATMENT

Replacement therapy with desiccated thyroid in patients with myxedema results in complete alleviation of the symptoms and manifestations of the disability and disappearance of all known metabolic aberrations. The goal in therapy is, of course, achievement of an euthyroid status, and this is best adjudged by clinical observation of the patient. An occasional patient cannot be restored completely, since attempts to achieve euthyroidism result in the appearance of angina pectoris, paroxysmal tachycardia or other distressing disability; in such patients suboptimal doses are necessary.

Once euthyroidism is achieved at a specific dosage, further alterations in requirement are not apparent. It seems unlikely, however, that in a healthy state the thyroid gland daily manufactures and releases to the body a constant amount of hormone; alterations in production and utilization of hormone probably occur during periods of stress, as has been suggested.<sup>153</sup> It is gratifying, then, that an unaltering daily dose of hormone provides successful replacement therapy.

*Preparations Available.* Desiccated thyroid, long available, is the preparation with which physicians have had greatest experience. Earlier variations in potency of different lots of desiccated thyroid were common but at present, due



to standardization of the powder according to its iodine content and its calorogenic potency, more uniform therapeutic results can be anticipated.

Despite the successful clinical use of desiccated thyroid, its economy and excellent standardization, crystalline thyroxine has been introduced commercially. Thyroxine is chemically extracted from thyroid glands; however, a new method of synthesis which may also be commercially feasible has been developed by Hems and his co-workers.<sup>154</sup> As a chemically pure substance thyroxine can be relied upon to give a uniform therapeutic result and this is, it appears, its main and only therapeutic advantage.

Although many analogs of thyroxine have been employed experimentally in myxedema,<sup>155</sup> only one, triiodothyronine, has received extensive study and clinical trials. In view of its unique metabolic properties, it may in some instances hold therapeutic advantage over desiccated thyroid and thyroxine.

*Rate of Response.* The rate of response to therapy with either desiccated thyroid or thyroxine is slow; the peak of metabolic action from a single dose of either of these preparations is obtained at about the fourth day following parenteral administration. The rate of therapeutic response obtained with triiodothyronine differs from that with desiccated thyroid or thyroxine. Triiodothyronine brings a rapid rise in metabolism, changes being readily detectable within six hours following a single dose given parenterally, and the maximum effect is reached about the second or third day.<sup>10,11</sup>

*Dosage.* A dosage of 96 mg. of desiccated thyroid daily maintains euthyroidism in most athyreotic patients. A large adult may require 128 or even 192 mg., whereas a small, frail person may require only 64 mg. daily. It seems likely that younger persons require more hormone than the elderly. Thus Wilkins<sup>42</sup> advocates 128 to 192 mg. daily in children in order to assure proper growth. In elderly athyreotic patients 64 mg. daily may suffice.

The dosage of thyroxine necessary to maintain euthyroidism in most athyreotic subjects is 300  $\mu$ g. daily; of triiodothyronine 100  $\mu$ g. daily.<sup>156</sup> These dosages refer to the levorotatory optical isomers, for the significant activity resides in these forms. Thyroxine and triiodothyronine, like desiccated thyroid, are effective when administered orally. During maintenance therapy the total daily dose may be taken at once, there being no advantage in divided doses.

As stated, the proper dosage level during treatment of myxedema is best estimated on clinical grounds. The return of the basal metabolic rate to normal and the lowering of the level of serum cholesterol are helpful laboratory aids. The level of serum protein-bound iodine rises considerably, of course, during exogenous administration of desiccated thyroid, and it has been reported that occasionally the level during therapy is above normal and is higher than might be anticipated by the clinical state of the patient and his basal metabolic rate.<sup>157</sup> This phenomenon is more likely to occur during treatment with thyroxine; values of protein-bound iodine of 11 or 12  $\mu$ g. per 100 ml. serum (or higher) have been recorded in patients who were obviously entirely euthyroid.<sup>156-158</sup> Striking, also, is the observation that during treatment with triiodothyronine the serum protein-bound iodine is less than normal at times when the patient is euthyroid.<sup>156,159,160</sup> Although this is due in part to the fact that triiodothyronine contains one less iodine atom per molecule than does thyroxine, the major explanation for the phenomenon is that triiodothyronine leaves the serum rapidly for cells.<sup>159</sup>

In uncomplicated hypothyroidism of short duration, initiation of treatment with a dose of hormone estimated to be the daily requirement is indicated. On the other hand, in patients with long-standing myxedema in whom tissue changes resulting from hormone lack are marked or in those patients with complications such as pericardial effusion, cardiac failure, hypertension, coronary artery insufficiency or pulmonary emphysema, more gradual restoration of metabolism to normal levels is advisable since rapid acceleration in metabolism may prove detrimental. The initial dose should be about one-quarter of the estimated daily requirement and the dosage usually can be increased at approximately weekly intervals until maximum benefit is achieved.

*Miscellaneous Considerations.* Differentiation of primary and secondary myxedema is important, for in the latter condition treatment with thyroid may fail to produce complete recovery. This is achieved only when other hormones, chiefly cortisone, are also administered. Moreover, the treatment of pituitary insufficiency with thyroid alone may be hazardous, since acceleration of metabolism may accentuate adrenal insufficiency. In the treatment of pituitary insufficiency replacement of thyroid hormone is as important



as that of adrenal cortical hormones. Werner<sup>161</sup> reports that a patient with pituitary insufficiency treated with cortisone showed no improvement until desiccated thyroid was also administered, following which recovery occurred.

The question is often discussed whether or not there is a clinical condition of chronic, partial hypothyroidism, a state between euthyroidism and myxedema. If such exists, it must be uncommon. Surely it may occur during the development of myxedema as well as during the initiation of treatment or with inadequate treatment of myxedema. In patients with doubtful hypothyroidism a therapeutic trial with desiccated thyroid is often helpful diagnostically. The metabolic response to therapy is specific in true hypothyroidism; signs of objective improvement must appear,<sup>162,163</sup> and the trial should be first conducted with placebo therapy.

Persons not showing clinical evidence of thyroid deficiency who have vague symptoms and a low metabolic rate which might suggest hypothyroidism usually have normal thyroid function as measured by other tests. That thyroid function is normal in such patients is indicated further by the fact that the symptoms and hypometabolism are not corrected by administration of desiccated thyroid. Yet Kurland and his associates<sup>164</sup> recently have reported improvement and an increase in metabolic rate in such subjects on administration of triiodothyronine, with or without thyroxine. Their studies do not exclude, however, the possibility that asymptomatic subjects having a normal metabolic rate might exhibit comparable increases in rate during therapy with the remarkably potent compound, triiodothyronine.

It has long been generally accepted that persons having normal thyroid function tolerate relatively large doses of desiccated thyroid without significant metabolic alteration, whereas athyreotic persons easily develop hyperthyroidism if the dose known to maintain euthyroidism is exceeded. Goldsmith and Stanbury<sup>165</sup> have cast doubt recently on this generalization.

#### SUMMARY

Deficiency of the thyroid hormone in man results in retardation of many bodily functions and metabolic processes. Despite extensive studies, both in man and animals, which have delineated and defined some of the metabolic aberrations occurring in myxedema, the exact

nature and mechanism of action of the thyroid hormone remain unidentified.

The diagnosis of myxedema is established by recognition of the symptoms and physical manifestations which result from lack of thyroid hormone as well as by several ancillary laboratory procedures. Myxedema is most often due to ablation or spontaneous idiopathic atrophy of the thyroid, although other specific mechanisms may lead to failure of production of thyroid hormone.

Treatment of thyroid deficiency consists of hormone replacement therapy with desiccated thyroid, thyroxine or triiodothyronine. Administration of one of these preparations daily in adequate dosage restores the patient to an apparently normal metabolic status. These medications are effective when administered orally. The results of therapy are gratifying.

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*End of Symposium on the Pathologic Physiology of Thyroid Diseases*

# Clinical Studies

## Functional Evaluation of Mitral Valvulotomy\*

### *Superiority of the Treadmill Exercise Tolerance Test to Clinical and Resting Hemodynamic Evaluations in Selecting Patients*

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ALTHOUGH the role of surgery as an adjunct to medical treatment of selected patients with mitral stenosis has been accepted by many,<sup>1,2</sup> it has been questioned by others.<sup>3</sup> Resolution of these differences of opinion may await the demonstration of significant differences in disability and longevity between operated and unoperated patients who have been followed up until death. Meanwhile it is pertinent to inquire whether or not better methods may be available for the more appropriate selection of patients for surgery. It is the purpose of this report to suggest that physical examination and physiologic measurements of patients performing a standard work-load afford a valuable aid to the physician who is responsible for recommending surgical treatment.

The quantitative effects on exercise tolerance of medical and surgical therapy of patients with mitral stenosis have been reported from this laboratory previously.<sup>4</sup> Patients have been followed up to three years, and more experience with this technic has been obtained. The relationship of functional capacity to exercise tolerance has been described,<sup>5</sup> as well as discrepancies between subjective and objective evaluation,<sup>6</sup> and changes in unoperated patients.<sup>7</sup> Now it is possible to determine, in retrospect, some of the factors which may affect prognosis.

#### MATERIAL AND METHODS

Fifty-two patients, ranging in age from nineteen to sixty-five with a mean of forty years when submitted to mitral valvulotomy, were classified at the end of the

study as: "improved," "unchanged," "worse" or "died," on the basis of the clinical course. Forty-nine patients had been submitted to surgery for relief of disabling mitral stenosis, two for prophylaxis against emboli and one for prophylaxis against congestive failure during any subsequent pregnancy. (One of the two patients with emboli and a third patient, a young woman, had had congestive heart failure previously, but disability was not the chief reason for surgery at this particular time.) Clinical and laboratory examinations, as previously described,<sup>4</sup> were made in all patients before and after surgery. The highest exercise tolerance score was selected (in order to eliminate the effects of any intercurrent illness) whenever more than one evaluation was available for any of the specified postoperative periods of observation. The number of studies were: preoperative evaluation, initial fifty-two patients; preoperative evaluation, final thirty-one patients; postoperative evaluation, one to three months thirty-one patients; postoperative evaluation, four to six months thirty patients; postoperative evaluation, seven to twelve months thirty-one patients; postoperative evaluation, thirteen to twenty-four months twenty-one patients; postoperative evaluation, twenty-five to thirty-six months thirteen patients. Fourteen patients were studied in all periods for two years.

In order to determine factors that may be associated with the subsequent clinical course, analyses were made of several clinical and laboratory observations before, during and following surgery. Relative degrees of variance of laboratory measurements were estimated from average coefficients of variation

$$(100 \times \text{standard deviation})$$

Mean

for seventy-eight tests in four patients who improved.

\* From the Departments of Medicine and Surgery, University of Washington, Seattle, Wash. These studies have been supported in part by Grant-in-Aid from the National Heart Institute of the National Institutes of Health, United States Public Health Service.



TABLE I  
CLINICAL EVALUATION PRIOR TO OPERATION

	Final Classification of Patients			
	Improved	Unchanged	Worse	Died
Number of patients . . . . .	29	15	3	5
Percentage distribution . . . . .	56%	29%	6%	9%
Mean age, years . . . . .	38	45	41	43
Duration of disability, years . . . . .	6	8	6	8
Incidence of				
Marked mitral stenosis* . . . . .	8	3	1	0
Moderate mitral stenosis . . . . .	21	12	2	5
Moderate mitral insufficiency . . . . .	14	6	2	4
Moderate pulmonic insufficiency . . . . .	8	3	1	2
Moderate aortic insufficiency . . . . .	3	2	0	1
Moderate tricuspid insufficiency . . . . .	1	1	2	1
Moderate aortic stenosis . . . . .	1	1	0	0
Auricular fibrillation . . . . .	14	7	3	2
1° AV block . . . . .	1	1	0	1
Right ventricular hypertrophy . . . . .	9	3	2	3
Left ventricular strain . . . . .	1	2	0	0
Heart failure . . . . .	12	5	2	3
Functional capacity				
Class I . . . . .	2	0	0	0
Class II . . . . .	3	2	0	0
Class III . . . . .	18	13	3	4
Class IV . . . . .	6	0	0	1

\* Severity of valvular disease refers to intensity of murmurs, i.e., grades I to III were rated as moderate, grades IV to VI as marked.

The clinical classification of functional capacity was in accord with the criteria of the New York Heart Association.<sup>8</sup> The subjective evaluation of the cardinal symptoms of dyspnea, fatigue, chest pain, palpitations, and so forth, which patients experienced during ordinary daily activity, were considered from three points of view: intensity, physical limitations and need for rest. Thus the rating for no symptoms was class I, for slight or occasional symptoms class II, for moderate symptoms class III and for marked symptoms (bed or chair existence) class IV. There were appreciable individual differences between patients with respect to conscious awareness of symptoms, as well as daily activities ordinarily encountered.

The exercise test utilized a treadmill ergometer\* operated at 1.7 m.p.h. on a 10 per cent grade; patients were walked to the limits of tolerance, or an arbitrary maximum of ten minutes. This work-load

\* A portable aluminum model, 18 by 49 inches in size, may be obtained from the Quinton Instrument Company, 1832 Shelby Street, Seattle, Washington.

increased the oxygen requirement three- to fourfold above the resting level.\*

Exercise tolerance has been expressed objectively in terms of the physical fitness index (PFI).<sup>4b</sup>

$$PFI = \frac{ERk}{C}$$

Where E = endurance, or duration of effort in minutes, up to a maximum of ten minutes,

R = "respiratory efficiency," or the average difference in oxygen concentration between inspired and mixed expired air when the latter is collected continuously and analyzed each minute.

C = cumulative heart rate for first three minutes of recovery, and

k = 100.

\* Reproducibility of results by this technic has been reported previously.<sup>4a</sup>

TABLE II  
HEMODYNAMIC OBSERVATIONS DURING CARDIAC CATHETERIZATION PREOPERATIVELY  
(MEAN VALUES)

	Final Classification of Patients			
	Improved	Unchanged	Worse	Died
Number of patients studied . . . . .	18	7	1	1
Arterial oxygen saturation, % . . . . .	90	91	74	86
Cardiac index, L/M <sup>2</sup> /min. . . . .	2.9	2.5	2.4	2.2
Stroke volume, ml. . . . .	47	45	56	93*
A-V oxygen difference, ml./L. . . . .	58	48	44	58
Right ventricular end-diastolic pressure, mm. Hg. . . . .	9	4	6	10
Pulmonary artery				
Systolic pressure, mm. Hg. . . . .	69	62	48	95
Diastolic pressure, mm. Hg. . . . .	33	26	22	30
Mean pressure, mm. Hg. . . . .	48	39	35	43
Pulmonary capillary pressure, mm. Hg. . . . .	29	26	20	26
Mitral valve orifice, cm. <sup>2</sup> (Gorlin <i>et al.</i> ) . . . . .	0.8	0.9	0.4	0.8

\* Heart rate reduced to 38 by digitalis.

Since ER = volume of oxygen utilized per 100 ml. of air ventilated during exercise, then PFI = ml. oxygen consumed per 10 L. of total exercise ventilation per heart beat for the first three minutes of the recovery period. This represents the ratio of efficiency of oxygen utilization during effort to rapidity of circulatory recovery; normal values range from 13 to 26 with a mean of 19.

In addition, symptoms, physical signs, blood pressure and precordial lead electrocardiogram (CB<sub>5</sub>) were also recorded each minute.

#### RESULTS

*Clinical Evaluation.* Twenty-nine of fifty-two patients were improved, fifteen were unchanged, three were worse, and five died following mitral valvulotomy. (Table I.) Since some patients changed both their attitudes and way of life postoperatively, minor differences in opinion occasionally occurred; this may have biased slightly the number of patients placed in the "unchanged" category. There were no significant differences in either average age or duration of disability among these four groups of pa-

tients. Approximately one-third of the patients in each group were underweight.

Three patients who were worse after operation had moderate cardiac enlargement and auricular fibrillation preoperatively. Five patients who died had only moderate (not marked) mitral stenosis; four also had moderate mitral insufficiency. Three of these five had congestive failure; four were classified as III-D, and one as IV-D. Possibly some of these patients were limited more by myocardial insufficiency than mitral valve obstruction. These criteria did not necessarily indicate a poor prognosis because similar findings were observed in some of the patients who improved.

*Hemodynamic Observations.* Except for slightly higher average cardiac indices in patients who improved ( $P = 0.7$ ), there were no differences in average resting hemodynamics among twenty-seven patients in the four groups who were catheterized. (Table II.) Thus when patients were selected primarily for disabling mitral stenosis, it was not possible to differentiate, by means of pulmonary arterial pressures at rest, between myocardial insufficiency and mitral

TABLE III  
CARDIORESPIRATORY OBSERVATIONS DURING STANDARD EXERCISE TOLERANCE TEST PREOPERATIVELY

	Classification of Patients			
	Improved	Unchanged	Worse	Died
Number of patients.....	29	15	3	5
Mean resting values:				
Heart rate.....	91	91	88	73
Systolic pressure, mm. Hg.....	115	113	120	124
Diastolic pressure, mm. Hg.....	75	71	73	74
Respiratory efficiency, vol. %.....	3.2	3.2	3.0	2.4
Incidence of ECG abnormalities during rest.....	8	3	2	3
Exercise:				
Incidence of dyspnea.....	11	6	1	2
Incidence of fatigue.....	3	2	1	0
Incidence of ECG abnormalities.....	19	15	3	3
Incidence of ST depression.....	12	12	2	3
Incidence of fall in systolic pressure.....	9	2	1	2
Endurance, minutes.....	6.0	9.5	10.0	2.7
Maximal heart rate.....	158	154	154	129
Maximal systolic pressure, mm. Hg.....	126	135	130	122
Maximal diastolic pressure, mm. Hg.....	81	85	77	80
Respiratory efficiency, vol. %.....	3.5	4.0	4.0	2.4
Recovery:				
Cumulative heart rate, 3 min.....	347	343	326	299
Incidence of ECG abnormalities.....	17	9	2	4
Incidence of systolic pressure rebound.....	8	5	2	3
Physical fitness index:				
Mean $\pm$ standard deviation.....	6.5 $\pm$ 4.9	11.6 $\pm$ 3.7	12.5 $\pm$ 3.1	1.9 $\pm$ .8

valve obstruction, as recently suggested by Harvey and associates.<sup>9</sup>

**Exercise Tolerance.** Patients who improved had very low endurance preoperatively; those who subsequently died exhibited more marked reduction in endurance, together with subnormal respiratory efficiency during both rest and exercise. (Table III.) In contrast, nearly normal exercise tolerance was observed preoperatively, on the average, in patients who were either unchanged or worse after surgery.

Patients who improved were more likely preoperatively to exhibit a fall in systolic pressure during exercise than patients who were unchanged.\* The latter group was more likely to show ST depression in the precordial electrocardiogram during early exercise than the former group. (Table III.) Other electrocardiographic changes occurred in some patients in each group.

\* Observe Figure 4 previously reported.<sup>4a</sup>

**Comparison of Functional Capacity and Exercise Tolerance.** Figure 1 shows the distribution of patients preoperatively with respect to both clinical classification of functional capacity and objective determinations of exercise tolerance. Furthermore the subsequent clinical course for the patients within each of the subdivisions is also shown. Thirty-eight of fifty-two patients fell in class III, seven in class IV, five in class II and two in class I. Exercise tolerance could be categorized in seven ranges of PFI values for the corresponding patients. Thus there were fifteen patients with PFI from 0.1 to 3.0, 11 in the range of 12.1 to 15.0 and smaller numbers in the intermediate ranges. This distribution was substantially different from that determined by clinical criteria involving a doubly subjective analysis on the part of both patient and physician.

The operative mortality was about 10 per cent for patients in class III and 14 per cent for patients in class IV. Expressed in relation to



exercise tolerance, the mortality experience was 33 per cent for patients with PFI under 3.0, and zero for those patients with PFI scores over 3.0.

Some patients in each of the four classes of functional capacity exhibited subsequent improvement after mitral valvulotomy. The chances of such improvement in patients with PFI values in the lower portion of the normal range was less than half and actually none for patients with PFI values over 15.0. (Fig. 1.)

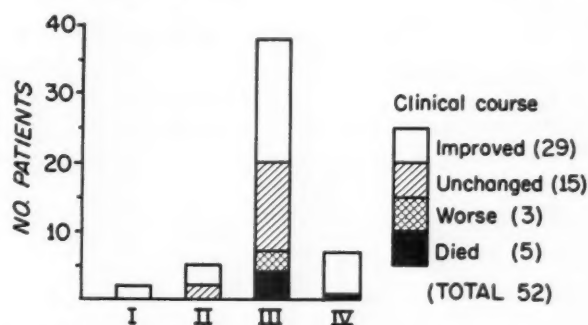
It is apparent, therefore, that objective determinations of exercise tolerance are superior to subjective appraisals of functional capacity since the procedure can be better standardized and there are more subdivisions in which to categorize patients. The probabilities of either operative mortality or survival without benefit can be more sharply defined.

**Operative Factors.** Hypotension during anesthesia and operation was quite likely to be associated with further difficulties in the early postoperative course. One patient died of ventricular fibrillation following hypotension incident to commissurotomy via the superior pulmonary vein.

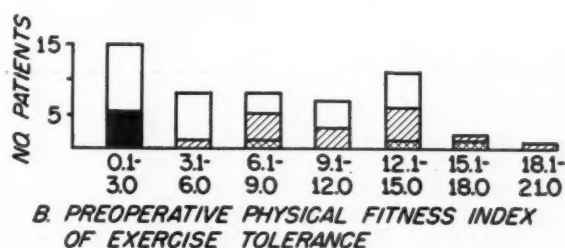
Two-thirds of the patients who improved had no mitral regurgitant jet at operation. If a systolic murmur of mitral insufficiency was recognized preoperatively, the chances were equal that a jet could be palpated at operation. If no systolic murmur was heard, there was only one chance in five of a jet being recognized. Three-fourths of the patients who improved had a successful anterolateral commissurotomy. In nearly two-thirds of the patients who were not improved only moderate dilatation of the mitral valve orifice could be accomplished, due to the nature of the valvular disorder, and many had a regurgitant jet prior to dilatation and attempted commissurotomy. (Table iv.)

Initially, the operative technic involved dilatation of the valve orifice with the palpating finger. An attempt was then made to fracture the anterolateral commissure. Except when the mitral valve orifice was ectopically located toward this commissure, no serious attempt was made to fracture the posteromedial commissure. Because the landmarks were usually obscure, and a small technical error could result in free regurgitation, no attempt was made to cut the latter commissure with a knife. Whenever finger fracture of the anterolateral commissure was incomplete, a variety of knives was used to extend the commissurotomy. In attempting

fracture, a tear of the posterior leaflets occurred in three patients. Although "dilatation" referred to partial enlargement of the orifice, autopsy examination revealed some fracture of both anterolateral and posteromedial commissures in such patients. Freely movable valve



A. PREOPERATIVE CLINICAL CLASSIFICATION OF FUNCTIONAL CAPACITY



B. PREOPERATIVE PHYSICAL FITNESS INDEX OF EXERCISE TOLERANCE

FIG. 1. Comparison of the distribution of patients according to preoperative functional capacity and preoperative exercise tolerance. The latter is expressed in terms of the physical fitness index. The subsequent clinical course after operation is indicated by the key.

leaflets were not obtained by dilatation, however. Mobility was also impaired by marked calcification even if adequate commissurotomy was achieved. Variations in pathologic involvement also conditioned technical accomplishment in other ways. Sometimes the auriculo-atrial junction was so small that a knife either could not be inserted or manipulated, in addition to the finger, without serious risk of rupture of the atrial wall. Occasionally the orifice of the auriculo-atrial junction was encroached upon by thrombi. When subvalvular stenosis or a deep funnel valve was encountered, only dilatation could be achieved, even with the use of knives. Similarly, fibroelastic valves with thickened edges sometimes failed to cut or fracture. While it has been hoped that the proportion of patients amenable to dilatation only would diminish with further experience, such has not been the case in actual practice.

TABLE IV  
SURGICAL OBSERVATIONS AND PROCEDURES

	Classification of Patients				
	Improved	Unchanged	Worse	Died	Totals
Number of patients.....	29	15	3	5	52
Mitral regurgitant jet:					
Absent.....	20	9	0	2	31
Created.....	1	1	1	0	3
Relieved.....	4	1	0	0	5
Persistent.....	4	4	2	3	13
					52
Operative procedure:					
Anterolateral commissurotomy.....	21	6	0	2	29
Dilatation of orifice*.....	6	8	2	3	19
Posterior valve rupture.....	2	1	1	0	4
					52
Positive auricular biopsy.....	5	0	1	0	6
Postcommissurotomy syndrome.....	7	4	1	0	12

\* See text.

Approximately one-half of the patients exhibited protracted convalescence, with labile and subnormal exercise tolerance as reported previously.<sup>4</sup> Many have presented symptoms and signs which could be variously interpreted as manifestations of the postcommissurotomy syndrome<sup>10</sup> or "carditis."<sup>5</sup> Sixteen patients who presented such features did not exhibit significantly different changes in exercise tolerance from the other patients over the ensuing year. At least one of every four patients continued to demonstrate recurrent episodes of heart failure precipitated by intercurrent respiratory infection, emotional disturbances, pregnancy, overwork, lack of adequate sodium restriction or inadequate digitalization. The majority require periodic medical supervision indefinitely.

The individual variations in the broad-spectrum of responses of patients selected for surgery can be illustrated by citing briefly two case histories.

One patient, J. B., with pulmonary fibrosis (with biopsy confirmation)<sup>4a</sup> in addition to mitral stenosis has shown surprising improvement up to three years after operation. She has gained weight, discontinued

all medical treatment and restrictions, and gradually lost the evidence of pulmonary fibrosis which was apparent by x-ray examination of the chest. She has written a monograph, "Second Wind," describing the remarkable success of cardiac surgery.

Another patient, B. W., had a marked mitral regurgitant jet at operation, biopsy of evidence of marked pancarditis, clinically apparent "carditis" postoperatively and gradual deterioration due to intractable heart failure. He died a year later; autopsy was reported to show a dilated heart with myocarditis, and marked stenosis of the valve.

There was no instance of peripheral embolization at surgery and only one patient has had recurrent peripheral emboli to date. The conversion of atrial fibrillation to normal sinus rhythm with quinidine was accompanied with an increase in exercise tolerance in a few patients. The effect of mitral valvulotomy on pregnancy in patients with mitral stenosis will be reported separately.<sup>11</sup>

*Evolution of Present Functional Capacity and Exercise Tolerance.* The changes in functional capacity of fourteen patients, who have been followed during each of the postoperative periods up to two years, are shown in Figure 2. Three of six patients in class IV survived and were

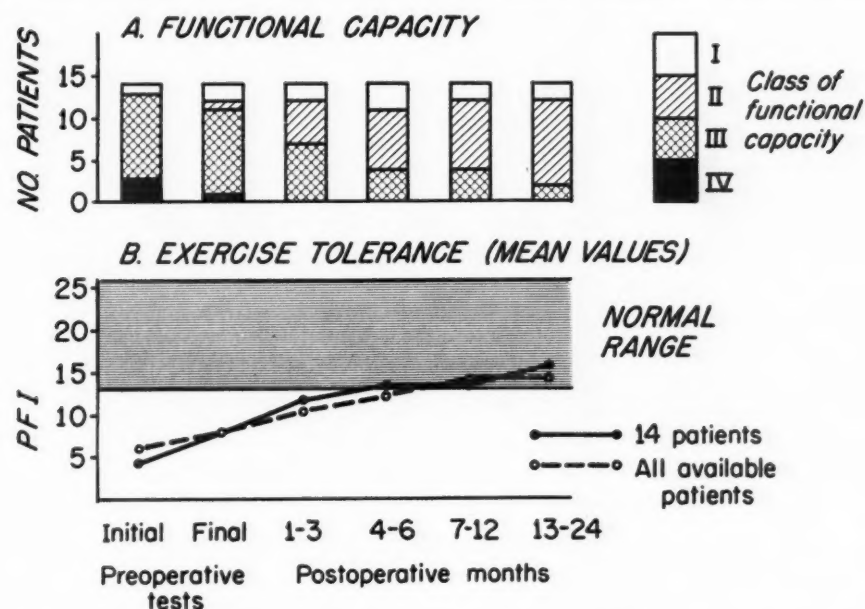


FIG. 2. Changes in the distribution of fourteen patients by classification of functional capacity. The average exercise tolerances, expressed in terms of the physical fitness index, are shown for these fourteen patients as well as for all patients studied during each of the periods of observation. Note the gradual improvement over the first two year postoperatively.

improved. There was an increase in the number of patients in class II. The consecutive mean PFI scores for these fourteen patients were similar to the average values for all patients who were available for study at any particular period of time. Gradual improvement in exercise tolerance was apparent over a year or more after operation; quantitatively it was only slightly greater than that observed in surviving unoperated patients.<sup>7</sup> This gradual rate of change may reflect adaptive changes in terms of recovery from apparent left ventricular atrophy,<sup>2</sup> regression of pulmonary arteriolar changes and, in some patients, regression of congestive changes in the liver.

A graphic analysis of these results is shown in Figure 3 in which mean values for the final preoperative exercise test are compared with those for the last postoperative test. Patients who improved had a decrease in mean heart rate during rest, exercise and recovery, together with increased endurance, respiratory efficiency and PFI. Essentially opposite effects were observed in patients who were either unchanged or worse.

Despite increased functional capacity and fairly definite decreases in incidence of dyspnea, heart failure and right ventricular hypertrophy (ECG), re-evaluation of the final clinical findings revealed slight increases in the incidence

of fatigue and cardiac enlargement. The incidence of underweight patients was reduced by one-half in those who were improved.

*Variance in Improved Patients.* The relative variance of several measurable factors was

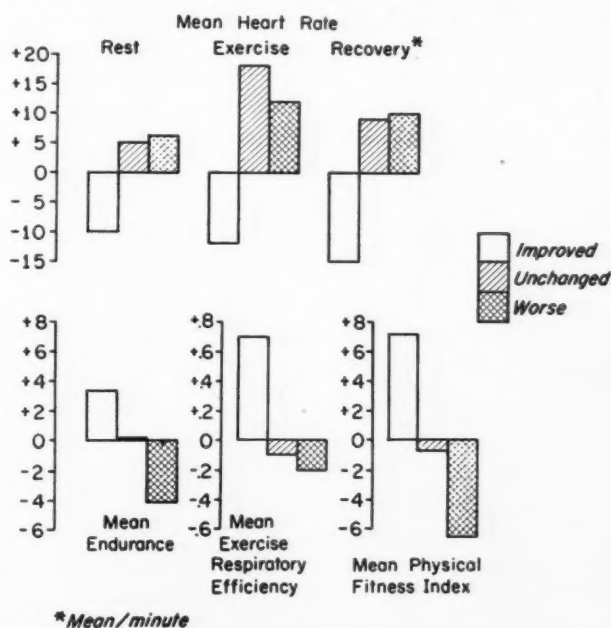


FIG. 3. Analysis of the changes in mean exercise tolerance of patients who were either improved, unchanged or worse following surgery to differentiate the relative importance, on the average, of the components of the physical fitness index. Note that changes were found in each of these variables.



TABLE V  
ANALYSIS OF VARIANCE  
(Expressed in Terms of Average Coefficient of Variation\*)

Rest		Exercise	
	%		%
Respiratory efficiency.....	33.1	Endurance.....	56.6
Circulation time.....	25.2	Intensity of dyspnea.....	49.1
Respiratory rate.....	16.3	PFI.....	46.0
Vital capacity.....	14.4	Intensity of fatigue.....	43.7
Heart rate.....	12.3	Respiratory efficiency.....	18.9
Blood pressure.....	7.6	Cumulative 3 min. recovery heart rate.....	16.5
Body weight.....	4.6	Systolic pressure.....	12.6
		Heart rate.....	10.3

$$* \text{Coefficient variation} = \frac{\text{Standard deviation} \times 100}{\text{Mean}}$$

(Based upon 78 tests before and after operation on 4 patients who improved.)

evaluated statistically by comparing average coefficients of variation. (Table v.)

With respect to resting measurements respiratory efficiency and circulation time (arm to tongue with decholin®) revealed more variance than vital capacity, heart rate or blood pressure. The least variable factor was body weight. The relative intensity of dyspnea and fatigue, as well as endurance and PFI for the standard exercise test, exhibited greater variance than any of the respiratory measurements. In other words, physical examination of patients in relation to a standard and physiologic form of exertion was considerably more instructive than merely examining patients at rest. Even rough quantitation of intensity of symptoms of dyspnea and of fatigue were meaningful when related to a standard work-load. Consequently one can obtain valuable information regarding exercise tolerance of patients with mitral stenosis if only two basic observations are recorded: (1) the intensity of dyspnea and fatigue (graded on a scale of none, slight, moderate or marked) and (2) the duration of time that patients can tolerate walking on a 10 per cent grade at 1.7 m.p.h. More complete appraisals are obtained if additional measurements are also made.

*Comparison of Operated and Unoperated Patients.* The serial mean changes in exercise tolerance are shown in Figure 4. They are compared, in terms of patients who were clinically improved, unchanged, worse or died, with the corresponding categories of unoperated patients previously described elsewhere.<sup>7</sup> Whereas the majority of operated patients were improved, none of the unoperated patients who survived for a year

after the initial evaluation exhibited as much increase, on the average, of exercise tolerance. On the other hand, nearly one-half of the unoperated patients who were considered "unchanged," and one-fifth who were considered "worse" by clinical criteria, actually showed an increase in average exercise tolerance. These data are considered to represent, as quantitatively as possible with methods now available, the role of cardiac surgery in partly relieving valve obstruction in patients with mitral stenosis. Significant changes in resting hemodynamics in fifteen patients recatheterized on an average of thirteen months after operation were limited to pulmonary capillary pressure and mitral valve orifice.<sup>5</sup>

#### COMMENTS

Salient factors which affect prognosis of mitral valvulotomy may be analyzed in three categories: preoperative, operative and post-operative. Preoperative factors focus on the patient's disability, as manifested by symptoms and limitations, due to mitral valve obstruction rather than on any other factors which may affect attitudes. They have dyspnea on effort, often orthopnea, and sometimes cough and hemoptysis (especially after intercourse). There are signs of pulmonary vascular engorgement, congestion and/or hypertension on examination. The severity of disability can be estimated from the subjective criteria which determine the functional capacity but may be more reliably measured objectively by means of the exercise tolerance test. Relative intensity of dyspnea and fatigue, endurance and PFI are most im-

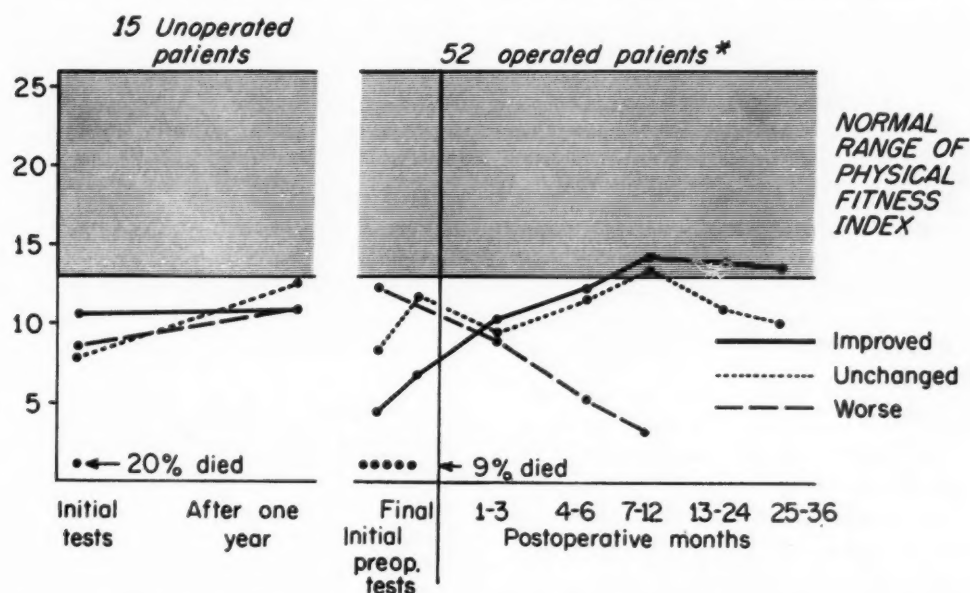


FIG. 4. Comparative effects of mitral valve surgery on mean exercise tolerance of patients who were clinically improved, unchanged or worse in relation to corresponding categories of patients not submitted to operation and re-evaluated again one year later. See text for details. Asterisk indicates the best tests for all available patients for each post-operative period.

portant; respiratory efficiency and abnormal electrocardiographic and blood pressure responses are also helpful when deviations from normal responses are encountered. The standard exercise tolerance test is most helpful in revealing which patients have a very low cardiac reserve. It is also helpful in defining more clearly the optimal chances of benefit from operation, as well as screening out patients who have normal or nearly normal performance despite various symptomatic complaints which may simulate those due to mitral valve obstruction. Occasionally, falsely high PFI scores are obtained from patients with auricular fibrillation who are digitalized to toxicity. Although the ventricular rate may be very rapid with exertion, it slows rapidly during recovery to levels simulating bradycardia. Contrariwise, falsely low PFI scores may be observed in patients who exhibit either marked apprehension with hyperventilation and tachycardia, or inappropriate motivation. Usually these persons are readily recognized by the observing physician.

This procedure of physical examination in relation to a standard work-load has helped the authors more than any other single clinical or laboratory observation in making a decision for or against surgical treatment in patients with symptoms due predominantly to mitral stenosis. The same principles have been applied equally well for other cardiac lesions. The same princi-

ples may be used for the evaluation of exercise tolerance by the physician in his office. The procedure makes use of a single step, such as that found on a regular examining table, and substitution of the respiratory rate for the respiratory efficiency.<sup>12</sup>

Translated into everyday experience, the patient with mitral stenosis who has difficulty climbing a single flight of stairs at a moderate pace, despite intensive medical treatment, may be nearly ideal for surgical treatment because the need is definite and the risk is not excessive. The patient who is unable to climb the stairs at all, because of the severity of heart disease, constitutes a real risk, whereas the patient who experiences no difficulty until he climbs several flights of stairs has little need of mechanical relief of obstruction and may show little benefit from surgical therapy. In our experience, operative mortality from any complications was limited to patients with very low exercise tolerance.

Operative factors which affected prognosis were technical inability to obtain an adequate commissurotomy in the presence of serious pathologic changes and the persistence of a regurgitant jet. In addition, hypotension during operation was often deleterious with respect to the immediate course and duration of convalescence.

Postoperative factors of importance during

the first few days were disturbances of fluids and electrolytes, blood coagulation and pulmonary disorders.<sup>13</sup> The cardiac patient with low reserve requires the physician to walk a tightrope between the hazards of hyponatremia and pulmonary edema. More effective and prolonged medical treatment preoperatively, as well as limiting fluids to 1.2 L. per diem (no intravenous infusions) postoperatively, are the salient controllable factors. The subsequent postoperative course is further affected by factors which may again precipitate heart failure, whether or not active "carditis" is present. Skillful medical supervision continues to be necessary. The important factor of time requires emphasis. Although occasionally patients exhibit dramatic improvement promptly, in our experience the majority require several months to a year or more to attain the maximal increase in functional capacity and exercise tolerance.

Whereas 92 per cent of patients believe they are improved when questioned, analysis of symptoms, signs, need for rest and medical treatment, limitations of recreational and occupational activities, and objective determination of exercise tolerance clearly reveal discrepancies between subjective and objective evaluation of surgical treatment.<sup>6</sup> In terms of changes in attitudes, the benefits of operation reported herein are equal or superior to some reports appearing in the literature.<sup>1,2</sup>

Further observation will be required to determine whether or not the slight decline in PFI which is now being observed in patients followed for three years represents evidence of restenosis of the mitral valve. McKusick recently reported such a case with autopsy evidence fifty-seven months after commissurotomy.<sup>14</sup> Although his patient had been taking sulfadiazine prophylaxis, persistently active carditis was undoubtedly present to account for the restenosis. Keyes and Lam have reported a possible case of recurrence of mitral stenosis (with hemodynamic documentation of a fall in left atrial pressure at operation) that required and benefited from a second operation eighteen months later.<sup>15</sup> Although many of our patients have shown marked deterioration in exercise tolerance transiently with either recurrent episodes of myocardial insufficiency or respiratory infection, the fact that exercise tolerance could be restored with medical treatment made us doubt the possibility of valvular restenosis. Nevertheless, the maximal PFI scores have

diminished perceptibly in patients observed during the third year after operation. It seems proper, therefore, to consider rheumatic heart disease in terms of chronic pancarditis with varying but often progressive manifestations during much of the lifetime of the patient. Mitral valvulotomy has a proper role in treatment but it is the responsibility of the physician to define it as carefully as possible for each patient.

#### SUMMARY

1. Further experience with fifty-two patients submitted to mitral valvulotomy has been surveyed with respect to those who were "improved," "unchanged," "worse" or "died" to determine any difference in preoperative clinical findings, resting hemodynamics, exercise tolerance, surgical observations and postoperative course which may affect prognosis.

2. Prognostic factors were discussed in relation to preoperative, operative and postoperative items of possible importance.

#### CONCLUSIONS

1. The standard exercise tolerance test affords more assistance in predicting the probable chances of either operative mortality, benefit, or no benefit from surgical treatment than the usual clinical criteria based upon examinations at rest of patients with mitral stenosis.

2. Patients with predominant mitral stenosis are more likely to benefit from mitral valve surgery if, despite intensive and prolonged medical treatment, they exhibit dyspnea and fatigue with exertion and disability due to pulmonary vascular engorgement, and objectively show impaired endurance, fall in systolic pressure and only a slight reduction in respiratory efficiency during effort.

3. If the physical fitness index (PFI) is between 3.0 and 6.0, the need for surgery is definite, the risk of operative mortality due to inadequate cardiac reserve is minimal, and the chances of benefit are maximal.

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# Pulmonary Valvular Stenosis with Intact Ventricular Septum\*

## *Results of the Brock Type Valvulotomy*

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EXPERIENCE with certain cardiac surgical procedures, and particularly with mitral commissurotomy, has shown that the degree of functional improvement noted by the patient does not always correlate well with the change in physiologic measurements as determined by pre- and postoperative studies. It would seem reasonable to assume that the same situation might exist in regard to the Brock valvulotomy and for that reason a group of patients has been studied by cardiac catheterization both before and after operation to determine how much change was produced in the right ventricular pressure as a result of surgical alteration of the pulmonary valve. The need for such studies has been

emphasized in a recent publication on the subject of surgery for pulmonary valvular stenosis from which Table 1, in abridged form, is taken.<sup>1</sup> The somewhat disappointing response observed by these authors following the Brock valvulotomy has been presented as an argument for the use of an open procedure in surgery for pulmonary stenosis.

### METHODS

Twenty patients of a total of forty-three who had been operated upon by the Brock technic were re-studied at various times postoperatively, the average interval being fifteen months. In all of these cases the preoperative diagnosis had been pulmonary valvular stenosis with intact ventricular septum. Seven of the

TABLE 1  
PHYSIOLOGIC RESULTS OF THE BROCK TYPE PULMONARY VALVULOTOMY. COLLECTED CASES<sup>1</sup>

Author	No. of Cases	Preoperative Right Ventricular Pressure Average (mm. Hg) (systolic)	Postoperative Right Ventricular Pressure (mm. Hg) (systolic)	Decrease Right Ventricular Pressure (mm. Hg) (systolic)
Lurie et al. ....	7	99	78	21
Bing et al. ....	8	127	92	35
Kirklin et al. ....	2	125	52	73
Galligan et al. ....	2	179	59	120
Soulie. ....	9	171	108	63
Humphreys et al. ....	3	193	75	118
Blount et al. ....	5	168	65	103
Total. ....	36	152	76	76

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patients in this group were cyanotic and the right-to-left shunt in these instances was thought to be through a patent foramen ovale or atrial septal defect since the right ventricular pressure was higher than the aortic systolic in this group. The patients ranged in age from three to twenty-six years at the time of surgery.

Each patient was examined, fluoroscopy of the heart was performed, and electrocardiograms were obtained. Heart catheterization was carried out according to standard technics. It was not possible to enter the pulmonary artery in every patient both before and after valvulotomy. Right ventricular pressures were recorded in each case.

#### RESULTS

The auscultatory findings changed very little, the systolic murmur and thrill remaining after valvulotomy. In a small number of patients an early diastolic blowing murmur developed along the left sternal border that was quite consistent with surgically produced pulmonary incompetence and sounded like the naturally occurring Graham Steell murmur.

No significant changes in the electrocardiogram were seen. The mean frontal plane electrical axis did shift from an average value of  $+108$  degrees to an average value of  $+95$  degrees. Minor changes in the T wave abnormalities noted before operation appeared but in no instance did a right ventricular hypertrophy pattern disappear. In one patient a right ventricular hypertrophy pattern noted before operation changed to complete right bundle branch block.

Changes in heart size as determined by the postero-anterior six-foot film of the chest were variable; increase, decrease and no change in heart size were seen. These did not correlate with the symptomatic improvement or the changes in right ventricular pressure.

The pulmonary artery pressure and the oxygen uptake were not measured in enough cases to allow any valid comparisons between the pre- and postoperative results. However, it appeared that no significant change had taken place in these two measurements in the few cases in which comparison could be made.

The measurement of most interest, the right ventricular systolic pressure, showed a significant alteration. (Table II.) For the entire group, the average right ventricular systolic pressure before operation was 116 mm. Hg whereas following surgery the average value was 56 mm. Hg. Of the entire group, five patients obviously

did not have any alteration in the right ventricular pressures, the average preoperative value being 94 mm. Hg and the postoperative value 93 mm. Hg. If this group of five patients is excluded from the total, the figures for the pre- and postoperative studies are 123 and 43 mm. Hg, respectively.

TABLE II  
RIGHT VENTRICULAR SYSTOLIC PRESSURE (MM. HG)

	Range		Average	Average Decrease
	Low	High		
<i>Twenty Cases</i>				
Before . . . . .	60	193	116	60
After . . . . .	25	122	56	..
<i>Fifteen Successful Cases</i>				
Before . . . . .	60	193	123	80
After . . . . .	25	80	43	..

TABLE III

Right Ventricular Systolic Pressure (mm. Hg)		Hemoglobin (gm./100 ml.)		Electrocardiogram* (degrees)		Arterial Saturation (%)	
Before	After	Before	After	Before	After	Before	After
130	31	23.2	13.2	117	100	74	97
180	25	16.0	16.3	...	...	78	84
130	66	20.0	15.0	107	100	70	80
144	35	18.7	15.7	135	97	73	91
105	30	18.5	14.1	...	...	...	...
120	80	18.5	15.8	...	...	78	90
193	49	25.0	17.0	122	108	79	93
Average 143	45	20.0	15.3	...	...	75	89

\* Mean frontal plane electrical axis.

The changes observed in the group of cyanotic patients are presented in detail in Table III. In addition to a marked drop in right ventricular systolic pressure, the hemoglobin value dropped from an average of 20.0 gm./100 ml. to a value of 15.3 gm./100 ml. Inversely, the femoral artery oxygen saturation rose from an average value of 75 per cent to an average of 89 per cent.

#### COMMENTS

Two points concerning the operative technic used in this group of cases are believed worthy



of emphasis. In each instance the area inferior to the valve was palpated to determine whether or not any degree of infundibular, or subvalvular, pulmonary stenosis was present. Secondly, following incision of the pulmonary valve with the Brock knife dilatation of the valve was carried out in a vigorous manner, using either an appropriately sized Hegar dilator or the surgeon's finger, depending on the size of the pulmonary valve ring and the root of the pulmonary artery. It is believed that these two maneuvers contributed in large measure to the generally good results observed in this series.

The question immediately arises as to why the operation was not successful in five of the cases, in view of the points mentioned. One obvious explanation is that neither the cutting nor the dilatation resulted in more than simple dilatation—that the valvulotome simply slipped through a fibrous pulmonary valve and did not create an incision. The second and perhaps more likely explanation is that infundibular pulmonary stenosis may well have been undetected despite the attempts made to exclude it. In none of these cases were pressure measurements made in the operating room and conceivably the five failures could have been detected in time to institute further corrective procedures had such measurements been made—a point emphasized by Brock in earlier publications.<sup>2</sup>

Usually it is not difficult to decide preoperatively whether or not the pulmonary stenosis is valvular or infundibular. When the typical poststenotic dilatation of the left main pulmonary trunk can be seen on fluoroscopy and when the pressure recordings made at the time of heart catheterization show an abrupt increase in pressure as the catheter is withdrawn from the pulmonary artery to the right ventricle, the diagnosis has been correct in each instance in the present series. However, if the roentgen picture is atypical, the abrupt change in pressures on withdrawing the cardiac catheter may suggest valvular stenosis although the lesion may in fact turn out to be infundibular. This might well be explained by the fact that the abruptness of change in pressure is related to the rapidity with which the catheter is withdrawn; also to the fact that the area of infundibular stenosis may be relatively well localized and immediately below the pulmonary valve so that the pressure changes do occur over a very short distance within the heart, and the "third ventricle" is so small that it

does not alter significantly the pressure recording. An additional point of importance is that both types of stenosis may occur in the same individual, making an accurate preoperative diagnosis difficult.

Especially gratifying was the response of the cyanotic group in whom the right-to-left shunt was thought to be at the atrial level. In these patients the drop in hemoglobin and the increase in arterial oxygen saturation accurately reflected the significant alterations in right ventricular pressure produced by valvulotomy.

Excluding the five cases in which no change occurred following surgery, the residual right ventricular pressure averaged 43 mm. Hg. This is not normal and in fact represents approximately twice the normal value obtained in most laboratories. Relative to this point, an important question remains unanswered, namely, does this magnitude of elevation in the right ventricular pressure represent an impossible burden for the right ventricular to bear or is it compatible with a long and active life. The answer is not as yet known and it has seemed reasonable that a residual right ventricular pressure nearer to normal would be advantageous to the patient. This has been the motivation for devising a more extensive surgical approach. Whether or not the simple Brock valvulotomy or an open operation involving a more drastic assault upon the pulmonary valve will prove to be preferable will have to await a long-term comparative study of two patient groups that have been subjected to the two surgical procedures. It would seem, however, that the Brock valvulotomy is in general a satisfactory operation for pulmonary valvular stenosis with an intact ventricular septum.

#### SUMMARY

1. In a group of twenty patients studied before and after the Brock valvulotomy, the average preoperative right ventricular systolic pressure was 116 mm. Hg, the average postoperative value 56 mm. Hg. Excluding five cases in which no significant change occurred, the average preoperative value was 123 and the postoperative value 43 mm. Hg. The five failures might be ascribed to the presence of undetected infundibular pulmonary stenosis or to the possibility that the valvulotome slipped through a fibrous valve without making an incision.

2. In a group of seven patients with right to

left shunt at the atrial level, the average pre-operative right ventricular systolic pressure was 143 mm. Hg and the postoperative 45 mm. Hg. In addition the hemoglobin dropped from 20.0 to 15.3 gm. per cent and the arterial oxygen saturation rose from 75 to 89 per cent.

3. Vigorous dilatation of the valve following incision with the valvulotome is deemed to be an

important determinant of a successful operative procedure.

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# A Long-Term Study of the Effect of Crude Rauwolfia Serpentina and of Its Alseroxylon Fraction in Patients with Hypertension\*

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THE value of extracts of Rauwolfia serpentina for lowering blood pressure in some patients with hypertension has been established.<sup>1-12</sup> This report describes results of a long-term study in thirty-six patients with complicated hypertension, i.e., obvious heart, kidney or brain damage, and in four relatively younger patients who presented a persistent elevation of diastolic blood pressure but without detectable complications.

## METHODS AND MATERIALS

Forty patients with well established hypertension are included. The cardiovascular renal status was evaluated carefully in all patients prior to therapy. The control blood pressure was determined from at least ten readings, over a period of three or more weeks. Usually the control level was determined from a considerably larger number of readings, and over a much longer period of time. Electrocardiograms, x-rays of the chest, urinalysis, blood counts, and kidney and liver function studies were obtained in most of the patients before, during and after the study.

Blood pressure readings during therapy were generally recorded by the same observer, under comparable circumstances, and at least three times weekly. All patients had at least ten readings per month. One patient had as many as four readings per day throughout eighty-nine weeks of therapy.

The total daily dose (1 mg. to 20 mg.) of the alseroxylon fraction† or the equivalent amount of crude Rauwolfia serpentina‡ was usually administered at bedtime. In several patients varying dose schedules were tried in an attempt to mitigate side actions.

† 'Rauwiloid,' Riker Laboratories, Inc., Los Angeles, California.

‡ 2 mg. alseroxylon fraction equivalent to approximately 125 mg. of crude Rauwolfia serpentina, of Indian origin.

Results are interpreted from the average systolic, diastolic and mean arterial pressures for the entire period, for each week, and for each four-week period during therapy. Mean arterial pressure was estimated by adding one-third of the pulse pressure to the diastolic pressure.

When applicable, the data were analyzed statistically by the "student test," by regression coefficients, by correlation coefficients, and by the Chi square. Results were considered significant when the P value was less than 0.02. Results reported as not significant gave P values greater than 0.10. P values between these two were not considered conclusive.

## RESULTS

*Blood Pressure Response.* The patients were divided arbitrarily into three groups, based on the response of their average mean arterial pressure. (Table I.) Group I consisted of eighteen patients (45 per cent of the total) whose average mean arterial pressure for any four-week period during therapy was at least 10 mm. Hg below the average mean arterial pressure of the control period. (Table I.) In thirteen of these patients (Cases 1 to 13) the final four-week determination of average mean arterial pressure was more than 20 mm. Hg below the control level; and in five (Cases 1 to 5) it was at least 30 mm. Hg below the control level. Sixteen of the twenty-six white patients (61.5 per cent) were in Group I, whereas there were only two of fourteen Negro patients (14.5 per cent) in this group.

The average systolic, diastolic and mean arterial pressure response curves of group I are illustrated in Figure 1. These curves were determined from the average pressures of each patient

\* From the Memorial Heart Laboratory, St. Mary's Hospital, Cincinnati, Ohio. This work was supported by a grant from the Dorothy B. Albers and Jeanette Albers Long Memorial Heart Fund.



TABLE 1  
FALL OF AVERAGE MEAN ARTERIAL PRESSURE (M.A.P.)

Case No. and Patient	Race, Age and Sex	Control Period			Treatment Period			Last Four Weeks' Therapy			Complications Associated with Hypertension*
		Duration (wk.)	Average M.A.P.	Average Blood Pressure	Duration (wk.)	Average M.A.P.	Dose Range (mg.)	Average Blood Pressure	Average M.A.P.	Dose Range (mg.)	
Group I, Greater Than 10 mm. Hg											
1, A. S.	W, 56, M	26	161	219/132	89	130	2-10	168/97	121	1	CF; A; HCV
2, B. C.	W, 51, F	40	152	218/119	89	116	1-10	164/89	114	2	CVA(X2); HE
3, R. B.	W, 58, M	62	149	200/110	86	112	2-10	150/84	106	2	A; HCV; MI; CF
4, S. W.	W, 56, M	10	135	193/106	57	112	6-10	161/76	104	2	CF; A; CRA; HCV
5, W. W.	W, 62, M	21	117	143/104	24	96	4	122/69	87	2	CF
6, A. T.	W, 76, F	4	130	186/102	33	105	10	161/70	100	10	CF; A
7, C. D.	W, 41, M	20	122	156/105	16	104	10	130/80	93	4	MI; CF; HCV
8, J. W.	W, 39, M	4	122	157/105	20	98	6	122/82	95	4	.....
9, R. W.	W, 45, M	6	130	171/109	16	114	6	140/83	103	4	.....
10, W. D.	N, 55, F	7	113	144/97	29	105	4-10	120/78	88	4	CF
11, M. R.	W, 40, M	16	148	202/121	66	122	8	162/105	124	8	MI(X2); CF; HCV
12, E. S.	W, 47, F	80	136	184/112	72	119	10	153/95	114	10	CF; A
13, L. B.	W, 62, M	146	132	185/106	68	133	4-6	188/73	111	4	CF; HCV
14, J. T.	W, 58, F	58	128	195/95	75	111	2-4	165/84	111	2	CF; A; MI; HCV
15, L. B.	W, 55, F	8	119	170/94	37	103	6	149/78	102	2	CF; HCV
16, S. W.	W, 43, M	110	112	145/95	56	101	2-4	132/81	98	2	CVA
17, S. A.	N, 56, M	8	139	198/109	15	131	8	169/105	126	6	CF; HCV
18, B. E.	W, 20, F	15	133	160/120	68	126	10-13	140/110	120	10	CRA
Group II, Between 5 and 10 mm. Hg											
19, B. B.	N, 30, F	11	150	190/130	17	144	10-12	185/116	141	12	CVA
20, L. R.	W, 59, F	12	131	192/101	61	124	10-14	184/93	123	4	CVA(X2); CF; HCV
21, N. R.	W, 41, M	32	126	159/109	20	117	6	148/103	118	6	.....
22, C. R.	W, 48, F	13	141	199/112	18	132	10	191/105	134	10	MI; A; CF
23, R. C.	N, 55, M	10	166	221/139	28	162	10	223/127	159	10	CVA; HCV
24, S. T.	N, 50, M	10	153	206/126	44	147	10-16	201/122	148	16	CVA; HCV
25, F. C.	W, 63, M	6	137	198/106	36	131	10	190/102	132	10	A; HCV
Group III, Less Than 5 mm. Hg											
26, L. W.	W, 70, F	13	141	212/106	56	137	4-10	213/101	138	6	CF; HCV
27, G. H.	W, 31, M	11	116	143/103	38	112	10	137/101	113	10	.....
28, R. W.	N, 37, F	21	127	159/111	44	122	5-8	162/106	125	8	CF†; CVA; HCV
29, L. F.	N, 54, M	8	157	241/115	52	154	4-20	236/116	156	20	CF; HCV
30, W. H.	N, 36, M	8	133	170/115	55	131	10-15	182/111	135	12	CF; HCV
31, M. R.	N, 32, F	32	156	208/130	10	158	10	205/134	158	10	CVA(X2); HCV; HE
32, M. M.	N, 46, F	16	124	173/99	44	115	4-8	189/95	126	6	CVA; HCV
33, C. R.	W, 62, M	12	115	176/85	61	117	2-6	198/77	117	2	CF
34, E. L.	N, 50, F	12	143	191/119	28	138	10	200/119	146	10	CVA; HE; HCV
35, H. W.	W, 55, M	32	119	187/85	66	120	2-6	202/83	123	6	CVA; CF†; A†; HCV
36, P. H.	W, 36, M	53	136	179/115	56	142	10	179/123	142	10	Patient died CVA†; HCV
37, M. W.	W, 61, M	30	119	160/97	44	120	6	175/102	126	2	MI; A; HCV; CF
38, L. S.	N, 72, F	28	146	222/108	20	151	10	246/108	154	10	CF; AMI; HCV
39, M. B.	N, 42, F	10	161	212/136	52	163	6-15	227/143	171	10	CVA; HCV
40, E. F.	N, 45, M	12	118	160/100	40	120	10-20	180/110	130	20	CVA; HCV; CF

\* Abbreviations are as follows: CF = congestive failure; A = angina; MI = myocardial infarction; CVA = cerebral vascular accident; CRA = chronic renal azotemia; HE = hypertensive encephalopathy; HCV = hypertensive cardiovascular disease.

† Occurred during therapy.

from each four-week period during therapy. A gradual decline of all three pressure values is shown for the first sixteen weeks. This is followed by a relatively flat curve. This plateau phase may be due, in part, to reduction in the total daily dose during therapy because of side effects. The regression coefficient calculated for the fall

of average mean arterial pressure was statistically significant.

Significant reductions in both diastolic and systolic blood pressures were obtained. The average reduction in diastolic pressure was 24 mm. Hg, the average fall in systolic pressure was 34 mm. Hg.

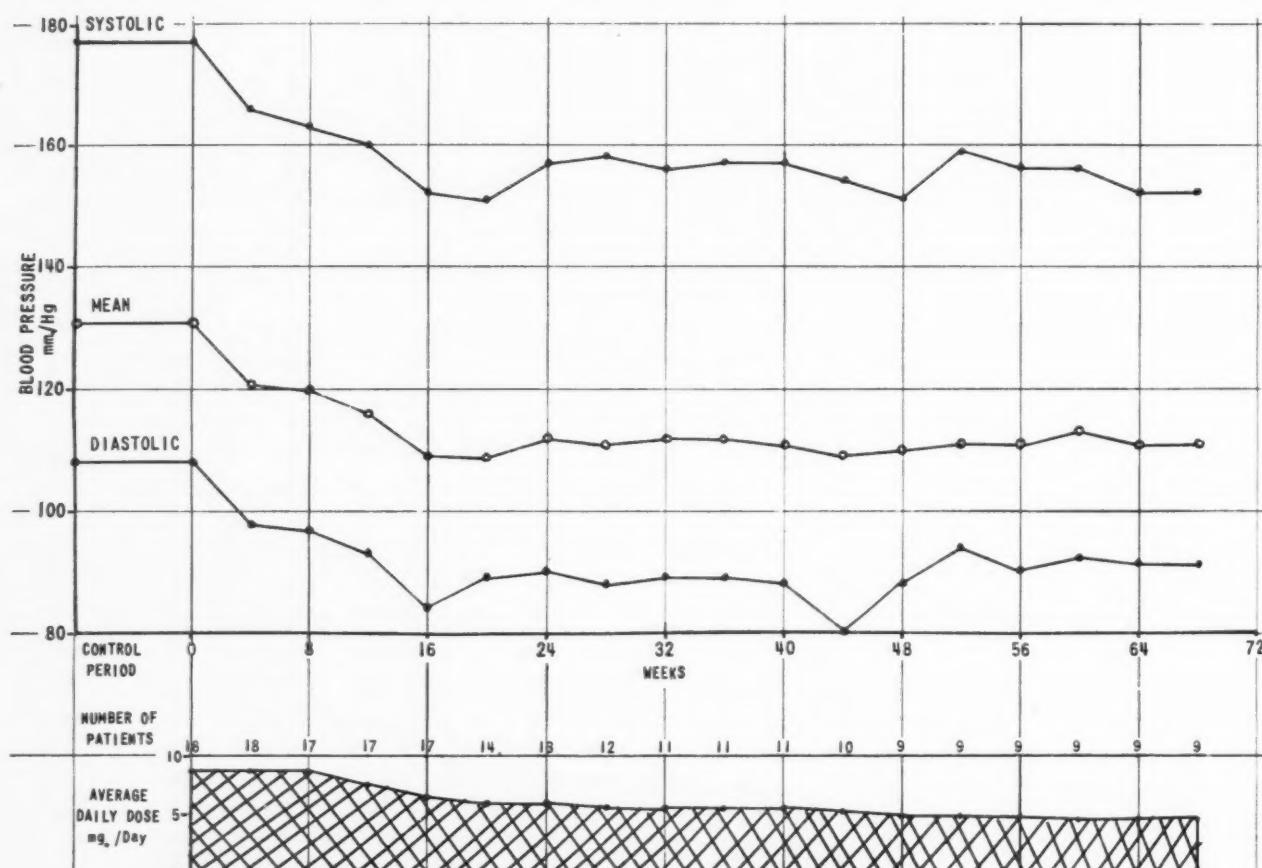


FIG. 1. Average blood pressure response.

In two patients (Cases 1 and 2) the pressure continued to fall for thirty-two and fifty-two weeks, respectively, and a continued fall was prevented only by repeated reductions of the daily dose. In one patient (Case 12) there was no further decline of blood pressure after a relatively rapid initial fall (two weeks) despite the continued use of a dose of 10 mg./day of alseroxylon. The response of the other patients was between these extremes.

In three patients temporary elevations of average mean arterial pressure (determined for four-week periods) occurred subsequent to the initial fall of 10 or more mm. Hg. In the remaining patients the fall of average mean arterial pressure of 10 or more mm. Hg was maintained after the initial fall.

Individual pressure readings usually reflected the average pressure response in a given patient. However, on occasion, single readings were considerably above the average pressure for the four-week period for each person. Thus it was evident that response to therapy could be determined only on the basis of multiple readings during control and treatment periods.

Group II consisted of seven patients whose average mean arterial pressure for any of the four-week study periods fell at least 5 mm. Hg but not more than 10 mm. Hg below the average mean arterial pressure of the control period.

Group III consisted of fifteen patients whose four-week average mean arterial pressures during therapy was not more than 5 mm. Hg below the control average mean arterial pressure.

*Satisfactory Therapeutic Response of Blood Pressure versus Dose (Table II).* A satisfactory therapeutic response was considered to have been achieved when the average diastolic pressure for a four-week study period was 90 mm. Hg or less. Such response was seen in thirteen of the eighteen patients in group I (Table IIa) but in none of the patients in groups II or III. The time of onset of a satisfactory therapeutic response varied from one month in two patients to as long as nine months in three patients. The average time of onset was three and a half months. In twelve of these thirteen patients the dose necessary to maintain a satisfactory therapeutic response was less than the initial dose, and varied from 2 to 6 mg. daily. An attempt to reduce the dose was not

TABLE II  
GROUP I

Case No. and Patient	Control Diastolic Pressure	Initial Dose (mg.)	Onset Fall—10 mm. Hg in Average M.A.P. (mo.)	Onset (mo.)	Diastolic Pressure	Dose to Maintain (mg.)	Tolerated Dose (mg.)	Limiting Factor
<i>a, Satisfactory Therapeutic Response (diastolic 90 or less)</i>								
1, A. S.	132	10	1	7	90	4	1	Sedation
2, B. C.	119	10	1	9	77	4	2	Sedation
3, R. B.	110	10	1	3	84	2	..	None
4, S. W.	106	10	3	4	81	4	1	Sedation
5, W. W.	104	6	3	3	81	2	2	Sedation
6, A. T.	102	8	1	3	73	10	..	None
7, C. D.	105	10	1	3	82	4	4	Sedation
8, J. W.	105	6	1	2	80	2	..	None
9, R. W.	109	10	2	3	83	4	..	None
10, W. D.	95	10	4	4	81	4	..	None
13, L. B.	106	10	1	1	79	6	4	Sedation
14, J. T.	95	4	4	4	70	2	..	None
15, L. B.	94	6	1	1	78	2	..	None
16, S. W.	95	4	4	5	80	2	..	None
<i>b, Unsatisfactory Therapeutic Response (diastolic pressure = lowest average)</i>								
11, M. R.	121	8	1	2	100	8	..	None
12, E. S.	112	10	2	4	94	10	..	None
17, S. A.	109	10	4	4	101	10	..	None
18, B. E.	120	10	5	5	109	10	..	None

made in the remaining patients. It is quite likely that in some patients the response could have been maintained with less than 2 mg. per day. Studies to determine this point are in progress in our clinic. Some recent studies, e.g., that of Lockett<sup>13</sup> indicate that 4 mg. of rauwiloid® daily (two tablets at bedtime) is the optimal dose. In three patients the dose required to maintain a satisfactory therapeutic response level was not well tolerated because of excessive sedation. In these patients a reduction in dose was followed by a moderate rise in pressure. Sedation persisted, but to a milder degree. Three additional patients complained of sedation with the dose necessary to maintain a satisfactory therapeutic level. However, this did not prevent their continuing medication. Side effects were not significant in the remaining seven patients.

In four patients in Group I (Table IIb) the diastolic pressure remained over 90 mm. Hg despite relatively large daily dosage throughout the period of therapy.

Nineteen of the twenty-two patients in groups II and III received at least 6 mg./day for a mini-

mum of twelve weeks. Sixteen patients received at least 10 mg./day for more than sixteen weeks. Seven of these patients received between 12 to 20 mg./day. Such large doses were given experimentally.

**Dosage Response.** Our data indicate the following: (1) Six mg. of alseroxylon daily is adequate early in therapy; the response at this dosage level may be more rapid than with a smaller initial dose, and a daily dose larger than 6 mg. will neither accelerate nor increase the response in the cases that do not respond favorably. (2) the total daily dose of rauwiloid is most conveniently administered at bedtime. Varying this dose schedule does not change the response or alter side actions significantly. (3) The full hypotensive response may not be obtained for at least sixteen weeks. If not present by the end of twenty weeks, it is unlikely that it will occur on Rauwolfia alone. (4) Symptomatic improvement and/or appearance of side effects are seen early, usually within ten days after rauwiloid is started. The appearance of either, or both, is no assurance that a hypotensive effect



TABLE III  
ELECTROCARDIOGRAPHIC FINDINGS BEFORE AND IMMEDIATELY AFTER STUDY\*

Electrocardiographic Diagnosis	Group I					Group II					Group III					Total				
	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During
Normal.....	7b	..	5	1a	..	2	..	2	..	1c	1	..	1	..	...	10	..	8	1	1
Left ventricular hypertrophy.....	6	2	4	..	1a	3	1	1	1	..	8	2	5	1	2dc	17	5	10	2	3
Old myocardial infarction.....	2	..	2	..	..	1	..	1	..	..	2	..	2	..	...	5	..	5	..	..
Recent myocardial infarction.....	2	2	..	..	..	..	..	..	..	..	..	..	..	..	...	2	2	..	..	1
Coronary insufficiency.....	..	..	..	..	1b	1	1c	..	..	..	1	1c	..	..	...	2	2	..	..	..
Borderline.....	..	..	..	..	..	..	..	..	..	..	1	..	..	..	...	1	..	..	1	..
Left bundle branch block.....	..	..	..	..	..	..	..	..	..	..	1	..	1	..	...	1	..	1	..	..

\* Key to this table is as follows: a, normal EKG before to left ventricular hypertrophy during study; b, normal to coronary insufficiency during to normal during study; c, coronary insufficiency prior to left ventricular hypertrophy during study; d, borderline prior to left ventricular hypertrophy after episode; e, coronary insufficiency prior to left ventricular hypertrophy after episode.

will also be obtained. Conversely, a satisfactory hypotensive effect is frequently achieved without side actions. (5) When a satisfactory hypotensive effect is achieved, namely, diastolic pressure of 90 mm. Hg or below, the daily dose should be reduced progressively. A satisfactory response may be maintained with as little as 1 mg. daily. (6) Some patients cannot tolerate a daily dose of 6 mg. without development of some side actions (notably sedation, nasal congestion and, occasionally, nightmares). These can usually be abolished by reduction of the daily dose. However, some of these side effects may recur later in a milder form, even on the reduced daily dosage level. Complete withdrawal of the drug results in a gradual rise in blood pressure and reappearance of uncomfortable subjective symptoms. (7) Readministration of rauwiloid, after withdrawal, results in prompt symptomatic improvement, frequently accompanied by return of the original side effects. This subjective improvement is accompanied with a prompt fall in blood pressure, which usually occurs much more rapidly than does the original response.

**Effect of Placebos and Drug Withdrawal.** Placebo studies were not carried out in all patients due to the nature of the study and the time necessary to evaluate response to the drug. Placebos were substituted for periods of two to four weeks in five patients who experienced undesirable side actions. In all five the undesirable side effects disappeared within a few days; within two weeks the blood pressure was considerably higher and undesirable subjective symptoms present prior to therapy returned. Within a week of resuming therapy the blood pressure was restored to a satisfactory therapeutic level, undesirable side effects returned, and undesirable subjective symptoms disappeared.

In three additional patients the drug was withdrawn after a satisfactory therapeutic response had been present for three months on a dosage of 2 mg./day. Within two weeks the pressure approximated the pretreatment levels. Two weeks after therapy was reinstituted the blood pressure fell to pre-withdrawal levels.

These results indicate that a maintenance dose of Rauwolfia is necessary to maintain the therapeutic effect. Further studies are indicated to establish this important point.

**Other Responses. Electrocardiograms:** Electrocardiograms were recorded in twenty-five patients prior to and after the study. (Table III.) Ten patients had normal electrocardiograms

prior to therapy. In one patient (group I) early evidence of left ventricular hypertrophy developed during therapy. The electrocardiogram of one patient (group I) who had acute coronary insufficiency immediately prior to therapy returned to normal within a few days. Subsequent records remained within normal limits. Another patient (group III) presented acute coronary insufficiency when therapy was started. Subsequent records revealed left ventricular hypertrophy.

Thirteen patients had left ventricular hypertrophy prior to therapy. The tracing was unchanged in seven patients after therapy. There was less evidence of deviation from normal in four, and more evidence of left ventricular hypertrophy in two.

Left ventricular hypertrophy developed in three patients during the treatment period, one from group I and two from group III. One patient of the latter group had a borderline tracing prior to treatment; the only pretreatment record in the other patient was recorded during an episode of acute coronary insufficiency.

Evidences of previous myocardial infarction or of coronary insufficiency were present in six tracings prior to therapy. The residual from the old infarcts did not change in two patients, evidence of the recent infarct continued to improve in two patients, and evidence of coronary insufficiency disappeared in two others.

A left bundle branch block in one patient did not change during therapy.

There were no significant changes noted in other components of the comparative tracings, for example, P-R, interval, QRS complex, Q-T interval and so forth.

*Heart rate:* Relative bradycardia was noted in the electrocardiograms of sixteen patients during therapy. There was little change of rate in several; in two a rate increase was noted. Bradycardia was seen as frequently in the unresponsive groups as in those with a favorable blood pressure response.

*X-rays:* X-rays of the chest were recorded in eighteen patients before and after study with Rauwolfia. (Table IV.)

*Size of heart:* This was evaluated according to the tables of Ungerleider and Clark. Values exceeding 10 per cent above the predicted norm were regarded as hypertrophy. Group I: the heart remained within normal limits in four patients before and after study. In three others

with hypertrophy the heart size showed a moderate decrease after study, namely, +15 per cent to +5 per cent, +15 per cent to +5 per cent, +15 per cent to +10 per cent. Groups II and III: the heart remained within normal limits in three patients. Eight others had hypertrophy prior to treatment. In three there was a reduction of heart size, namely, +25 per cent to +15 per cent (two patients); +20 per cent to +5 per cent (one patient). In five the heart size remained the same, namely, +30 per cent (one patient); +25 per cent (four patients).

In general, hearts which were markedly enlarged prior to therapy did not decrease significantly in size during therapy; hearts which were moderately enlarged showed some decrease in size, and hearts which were normal remained so. No x-ray evidence of heart enlargement was noted in any of the patients while they were on therapy.

*Size of aorta:* This was evaluated according to the criteria of Sheridan. Group I: the transverse diameter of the aorta was normal prior to and following therapy in three patients. In four the transverse diameter was increased prior to treatment (54 mm. versus predicted normal 49 mm.; 61/58, 61/52, 63/49). The transverse diameter did not change following therapy. In one patient (Case I) the transverse diameter prior to therapy was 90 mm. (predicted normal —63); this decreased to 80 mm. after therapy. There was no evidence of syphilis in any of these patients. Groups II and III: the transverse diameter of the aorta was normal in four patients prior to and following therapy. In three the transverse diameter was enlarged prior to treatment and did not change (81 mm./61 predicted normal; 66/56; 68/61). In two patients (Cases 29 and 24) there was prominent enlargement after therapy; 59 mm. to 71/56 predicted normal; (85 mm. to 94/64). There was a marked decrease in the aortic transverse diameter in the remaining patient (82 mm. to 53/56 mm. predicted normal).

A positive reaction to the Wassermann test was obtained in one patient in whom there was a markedly enlarged aorta which did not change (81 mm.), and in the patient who had an enlargement of the aorta from 59 mm. to 71 mm. during therapy. A non-contributory history and a negative reaction to the Wassermann test were obtained from the other patient in whom the aorta enlarged from 85 mm. to 94 mm. A negative reaction to the Wassermann test and a

TABLE IV  
FINDINGS IN X-RAYS OF THE CHEST BEFORE AND IMMEDIATELY AFTER STUDY

	Group I				Groups II and III				Total			
	Present Prior	No Change	Decreased Size	Increased Size	Present Prior	No Change	Decreased Size	Increased Size	Present Prior	No Change	Decreased Size	Increased Size
Heart size:												
Normal.....	4	4	..	..	3	3	..	..	7	7	..	..
+15 to 20%.....	3	..	3	..	1	..	1	..	4	..	4	..
+20 to 30%.....	..	..	..	..	7	5	2	..	7	5	2	..
Aorta:												
Normal.....	3	3	..	..	4	4	..	..	7	7	..	..
Moderately enlarged.....	3	3	..	..	2	2	..	..	5	5	..	..
Markedly enlarged.....	1	..	1	..	4	1	1	2	5*	1	2	2

\* Wassermann test gave positive results in two patients; one did not change; one enlarged.

non-contributory history were also obtained in the patient in whom the aorta decreased markedly during therapy.

*Renal function studies:* One or more renal studies, namely, urinalysis, blood urea nitrogen test, and phenolsulfonphthalein excretion studies were performed in thirty patients prior to and following therapy. There was no evidence that renal function was impaired significantly by the drug in any patient.

*Liver function tests:* Cephalin flocculation and thymol turbidity tests were performed in fourteen patients following the study. All were within normal limits.

Complete blood counts in thirty patients, before and after therapy, yielded no evidence of disturbance of hematopoietic function.

#### STATISTICAL ANALYSES OF BLOOD PRESSURE

Statistical analyses marked with asterisk were based on the results obtained from the first thirty-three cases studied. Analyses not marked included the entire series.

1. There was no relation between the level of the control mean arterial pressure and the occurrence of fall in blood pressure or the degree of such decline, during therapy.

2.\* There was no significant difference in response to rauwiloid between the group of sixteen patients whose control average mean arterial pressure was more than 136 mm. Hg and the group of sixteen patients whose control average mean arterial pressure was less than 136 mm. Hg.

3.\* There was no significant difference between the control average mean arterial pressure

(134.0 mm. Hg) of the patients in group I who responded well and the control average mean arterial pressure (139.4 mm. Hg) of patients in groups II and III who did not respond adequately.

4.\* In group I no significant correlation was noted between the level of mean arterial pressure during the control period (range 122–160 mm. Hg) and the degree of fall which occurred during therapy.

5. There was no relation between the age or sex of the patient and the response of blood pressure during therapy.

6.\* There was no significant difference between the average age of patients in the favorable group (50.2 years) and the average age of the remaining patients (49 years).

7.\* Within group I (favorable response) there was no significant correlation between the age of the patient and the degree or rapidity of onset of response.

8.\* There was no significant difference between the distribution of men and women in groups I, II and III. Furthermore there was no significant difference in the average fall of blood pressure of men versus women in the entire series.

9.\* Rauwiloid and total Rauwolfia serpentina were equally effective hypotensive agents.

#### RACIAL DIFFERENCES

There was a significant difference in the blood pressure response between Negro and white patients. (1) Sixteen of the twenty-six white patients, but only two of the fourteen Negro patients were in group I. This difference was



significant and could not be explained on the basis of age, sex or degree of hypertension. (2) Six of the ten white clinic patients, but only two of the fourteen Negro clinic patients were in group I. This difference was significant. (3) There was a significantly higher frequency of cerebral complications in Negro patients (nine of fourteen) as opposed to white patients (five of twenty-six). Coronary artery disease occurred significantly more often in white patients (twelve of twenty-six) than in Negroes (one of fourteen). It is possible that the difference between the response of white and Negro patients was related in some manner to the higher incidence of cerebral complications in Negro patients, as well as of coronary artery disease in white patients. (4) During therapy no significant difference was noted in the response of blood pressure of white patients receiving either clinic or private care. Six of the ten white clinic patients were in group I, two in group II and two in group III. Ten of the sixteen white patients receiving private care were in group I, two in group II and four in group III.

#### DISCUSSION

*Major General Subjective Changes during Therapy.* The value of Rauwolfia serpentina in hypertension is not limited to its hypotensive effect. Relief from the unpleasant symptoms so frequently associated with hypertension occurred in a high percentage of patients. These changes are listed in Table V. It is noteworthy that beneficial changes in symptoms occurred as frequently in patients who had little or no hypotensive response (groups II and III) as in the patients with a favorable response (group I). This symptomatic improvement was usually noted within the first week of therapy. In group I these changes preceded the fall in blood pressure. In the entire series the occurrence or degree of any of these subjective changes could not be correlated with the subsequent response of blood pressure. In general, larger doses produced greater symptomatic changes in individual patients.

*Desirable Effects. Relief of intermittent flushing of face, neck and upper chest:* Flushing was present in thirteen patients prior to therapy. Marked improvement was seen in twelve patients within a week of therapy, and questionable improvement occurred in the remaining case. In one instance (Case 12) the flushing was dramatic and

embarrassing, and would occur with only slight provocation. After three days of therapy (10 mg./day) flushing could not be reproduced even though the patient was presented repeatedly to study groups where deliberate attempts were made to initiate flushing. Case 20 (group III) had complete remission of marked flushing. Case 36 (group III) had marked improvement of flushing without any change in blood pressure during therapy.

The change from a flushed and flustered appearance to one of cool calm was one of the most striking and gratifying results obtained.

*Relief of throbbing and visible pulsations of arteries of neck and head:* This undesirable symptom subsided markedly in twelve of thirteen patients in whom it was present prior to therapy. In Case 1 striking and annoying pulsations of dilated and tortuous carotid arteries had been present for years. After a week of therapy abnormal pulsations could not be detected clinically, and associated symptoms were abolished completely. This favorable result persisted throughout eighty-nine weeks of therapy. Within ten days of discontinuing rauwiloid (1 mg./day) objective and subjective evidences of abnormal carotid pulsations returned, and the blood pressure started to rise. Resumption of the 1 mg./day dose again afforded relief, within one week.

*Decrease in headaches:* Reduction in both the frequency and severity of headaches was reported by twenty of twenty-two patients who were bothered severely by this complaint prior to therapy. In three patients (Cases 12, 18 and 36) disabling throbbing headaches were experienced practically every morning prior to treatment. These headaches were not affected by aspirin, were aided only partially by codeine, and on occasion were so severe that stronger narcotics were required. During rauwiloid therapy the headaches in Cases 12 and 36 decreased markedly in intensity, and could usually be controlled by aspirin alone. In Case 18 (a patient with chronic pyelonephritis and chronic azotemia) the headaches subsided even though the blood urea nitrogen remained elevated.

Two patients who had frequent attacks of migraine prior to therapy reported no recurrences while receiving treatment.

*Relief of anxiety:* Fourteen of the fifteen patients who had long shown evidences of anxiety prior to therapy had marked improvement of objective signs and subjective symptoms follow-

TABLE V  
COMPARISON OF MAJOR SUBJECTIVE CHANGES BEFORE AND DURING THERAPY

	Group I					Group II					Group III					Total				
	Pres-ent Prior	Im-proved	Same	Worse	Oc-curred Dur-ing	Pres-ent Prior	Im-proved	Same	Worse	Oc-curred Dur-ing	Pres-ent Prior	Im-proved	Same	Worse	Oc-curred Dur-ing	Pres-ent Prior	Im-proved	Same	Worse	Oc-curred Dur-ing
Desirable improvements:																				
Flushing face.....	7	7	..	..	..	2	1	1	..	..	4	4	..	..	..	13	12	1	..	..
Throbbing head.....	6	6	..	..	..	3	3	..	..	..	4	3	..	..	..	13	12	1	..	..
Headache.....	9	9	..	..	..	5	4	1	..	..	8	7	1	..	..	22	20	2	..	..
Palpitation.....	5	4	1	..	..	3	3	..	..	..	4	1	1	..	..	7	5	2	..	..
Anxiety.....	8	7	..	..	1	3	..	..	..	1	4	4	..	..	6	15	14	..	1	2
Ability to sleep.....	..	..	..	..	8	..	..	..	..	6	..	3	2	..	..	..	3	2	..	..
Constipation.....	..	..	..	..	1	..	..	..	..	..	5	..	..	..	..	5	..	..	..	1
Undesirable side effects:																				
Sedation.....	..	..	..	..	14	..	..	..	..	4	..	..	..	..	9	..	..	..	..	27
Inability to concentrate.....	..	..	..	..	7	..	..	..	..	1	..	..	..	..	4	..	..	..	..	12
Nightmares.....	..	..	..	..	3	..	..	..	..	1	..	..	..	..	3	..	..	..	..	7
Nasal congestion.....	..	..	..	..	5	..	..	..	..	2	..	1	1	..	5	..	1	1	1	12
Diarrhea or loose stool.....	1	..	1	..	3	..	..	..	..	2	2	1	..	..	7	4	..	..	..	7
Weight gain.....	..	..	..	..	3	..	..	..	..	3	..	..	..	..	2	..	..	..	..	13

ing therapy. In two others transient evidences of anxiety state developed during therapy.

*Disappearance of palpitation:* Complete disappearance of palpitation was reported by five of seven patients in whom this had been an annoying complication prior to therapy. An additional patient, without hypertension and not included in this series, had palpitation to such a degree that he could count his heart beat accurately at all times, and in any position. This had persisted for eighteen months and did not respond to any previous therapy, for example, quinidine, barbiturates and procaine amide. One week after starting rauwiloid, 10 mg./day, this symptom disappeared. The drug was discontinued because of side effects. During the next six days the palpitation returned gradually to pretreatment status.

*Improved ability to sleep:* Twenty patients reported improvement in their ability to sleep. The occurrence of nightmares in six other patients was, however, an undesirable side effect.

*Relief of constipation:* Constipation was alleviated in three of five patients. There was no significant improvement in the other two, and in one patient constipation developed while on therapy.

*Undesirable Effects. Sedation:* The most undesirable side effect is sedation, sometimes to the point of apathy. It was present to a significant degree in twenty-seven patients and was the principal limiting factor in toleration of the total daily dose. It occurred early in therapy, before any change in blood pressure, and was present with equal frequency and intensity in all three groups. The occurrence of sedation was, apparently, an individual problem in each patient. Some patients in group I had no sedative effects despite a marked fall in blood pressure, and two patients in group III received 20 mm./day for more than three months without a significant sedative effect. Sedation, when present, was definitely related to the daily dose. In two patients (Case 1 and 2) a sedative effect present earlier with 10 mg./day persisted throughout therapy even though the total dose was lowered as the blood pressure continued to fall. In Case 2 (four blood pressure readings per day throughout the study) the level of the blood pressure was related directly to the daily dose (below 4 mg./day) even after fifty-two weeks of therapy. An average blood pressure of 120/70 was maintained with 4 mg. of rauwiloid per day, 164/89 with 2 mg./day, 170/100 with 1 mg./day.

Placebo therapy resulted in a rise of average blood pressure to 220/100 within two weeks. Within a week of resuming therapy the blood pressure returned to the levels described, again dependent directly on the total dose. The dose of 4 mg./day, however, resulted in marked apathy. The 2 mg./day was associated with a definite but acceptable sedative effect.

A mild degree of sedation proved undesirable in some patients, particularly those doing executive work. Some of these patients complained frequently of inability to concentrate and/or to maintain a train of thought, resulting in impairment of executive abilities. In these patients various dosage schedules were tried without success (for example, total dose in the morning; before the evening meal; divided doses and so forth).

**Nightmares:** This unusual complaint was reported by seven patients while on therapy. The nightmares disappeared promptly when therapy was discontinued. One patient reported nightmares the first night after one 6 mg. dose of rauwiloid. Another received 10 mg./day for twenty days before the first nightmare occurred. All patients experiencing nightmares had subsequent therapy with a smaller dose without the occurrence of nightmares. Four had nightmares while on crude Rauwolfia therapy; these did not recur with comparable doses of rauwiloid. Interestingly enough the nightmares were usually horrible (for example, lying on a railroad track with a train approaching, swallowing a snake, stabbing somebody in the throat). One patient stated, "I wouldn't mind it if I had an occasional light comedy or if there were girls, but this succession of tragedies is getting me down." One patient reported scintillating dreams which were entirely acceptable.

Nightmares were not reported by any of the twenty patients who experienced increased ability to sleep. There was no apparent relation between the occurrence of nightmares, the social level of the patient, or the type of daily activity.

**Nasal congestion and/or dryness of nose and throat:** These symptoms developed in twelve patients during therapy. In four congestion was so marked that the daily dose was reduced. Complete nasal obstruction occurred in one patient with nasal polyps, necessitating surgical removal. Of the four patients in whom there was nasal congestion prior to therapy, two remained the same, one improved and one became worse.

**Diarrhea or loose stool:** Diarrhea and/or loose

TABLE VI  
COMPLICATIONS OF HYPERTENSION BEFORE AND DURING THERAPY

	Group I					Group II					Group III					Total				
	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During	Present Prior	Improved	Same	Worse	Occurred During
Coronary artery disease:																				
Angina.....	8	8	..	..	..	2	2	..	..	..	2	2	..	..	1	12	12	..	..	1
Old myocardial infarction.....	2	..	2	..	..	1	..	1	..	..	2	..	2	..	..	5	..	5	..	..
Recent myocardial infarction.....	2	2	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2	..	..	..
Hypertensive cardiovascular disease..	9	5	1	..	1	4	2	1	..	..	13	3	6	2	1	26	10	8	2	2
Comparison not available.....			(3)					(1)					(2)					(6)		
Congestive failure.....	13	..	13	..	..	2	..	2	..	..	7	..	7	..	2	22	..	22	..	2
Cerebrovascular accident.....	2	2	..	..	..	4	3	..	1	..	7	7	..	..	1	13	12	..	1	1
Renal azotemia.....	2	..	2	..	..	..	..	..	..	..	..	..	..	..	..	2	..	2	..	..



stool were reported frequently during the period when patients were receiving the crude form of the drug. Patients commented occasionally about loose stools while receiving the alseroxylon fraction but never to such a degree that it was necessary to change the dosage.

*Peripheral neuritis:* In one patient receiving 500 mg./day of crude rauwolfia peripheral neuritis developed which was manifested by pain, paresthesia and objective stocking and glove hypesthesia of all extremities within ten days. The nutritional status was adequate. The objective and subjective findings gradually subsided after the drug was discontinued. This patient subsequently received rauwiloid, 10 mg./day, and evidences of neuritis did not recur. In another patient, not in this series, similar peripheral neuritis developed one week after administration of Rauwiloid 10 mg./day. Again the nutritional status was good. The neuritis subsided gradually after the drug was discontinued. The course of remission apparently was not accelerated by thiamine. Five other patients complained of pain and paresthesias of one or more extremities occurring during sleep. These sensations were described as similar to the leg or arm "going to sleep," but were different in that prolonged massage (up to three hours) was necessary for complete relief.

*Menstrual changes:* Attention was directed to these changes by three young women, ages nineteen to twenty-four, who received rauwiloid, 10 mg./day, to study the possible beneficial effect in pulmonary hypertension associated with congenital heart disease. Amenorrhea for five months occurred in one, and in the other two patients the periods were reduced from six to three days, with a lessened flow. A recheck of the patients in this series indicated a decrease of time from five to two days in Case 18 (twenty year old girl).

#### COMPLICATIONS ASSOCIATED WITH HYPERTENSION BEFORE AND DURING THERAPY

The incidence of the complications associated with hypertension are listed in Table VI. Some degree of complications was present in thirty-six of the forty patients.

We have classified the complications broadly as cardiac, cerebral and renal.

There was no significant difference in the incidence of cardiac complications in the three groups. These patients were then subdivided

according to the presence of hypertensive cardiovascular disease, coronary artery disease and/or congestive failure. Coronary artery disease was more frequent in group I whereas hypertensive cardiovascular disease was more frequent in groups II and III. On analysis these differences were not conclusive. No significant difference in response could be attributed to the presence of congestive failure prior to therapy.

Cerebral complications were more frequent in groups II and III but, on analysis, the results were not significant. There were too few cases with hypertensive encephalopathy to permit analytical differentiation.

Important renal complications occurred in only two patients. Statistical analysis was not feasible.

In this series there were four patients (average age of thirty-nine) without complications. Normotensive blood pressure resulted in two. Therapy in one had to be discontinued because of side effects. There was no response in the other patient who received 10 mg./day for thirty-eight weeks. Six of seven additional patients under the age of forty who were not included in this study have had normotensive response.

*Coronary Artery Disease.* The diagnosis of coronary artery disease was limited to patients who had obvious angina or who presented a proved episode of myocardial infarction or coronary insufficiency. Coronary artery disease was diagnosed in thirteen of the forty patients prior to therapy.

Twelve patients had angina. Nine of these had no recurrence of angina while taking rauwiloid. In the three other patients marked improvement was noted in that episodes of angina became occasional instead of frequent.

In one patient (Case 35) mild angina developed during the fifty-fifth week of treatment. The angina was neither aggravated nor relieved, even though rauwiloid was continued for an additional nine weeks during this study. Relief from angina occurred in four patients in groups II and III, despite absence of a significant fall in blood pressure.

In six patients there were seven proved episodes of myocardial infarction prior to therapy. Four patients with old infarctions and a stabilized electrocardiographic pattern showed no significant clinical or electrocardiographic change during therapy. One patient with an old infarct had a recent infarct two months before

therapy, and another patient had an infarct three weeks prior to therapy. Prior to institution of rauwiloid the progress of the latter patient was unsatisfactory in that angina continued despite carefully supervised treatment. Another patient had an episode of coronary insufficiency with electrocardiographic changes immediately prior to treatment. These three patients received 10 mg. rauwiloid/day. In all three the electrocardiogram improved during therapy, and a hypotensive effect was also obtained. The patient who had suffered an infarction three weeks before had complete disappearance of angina and improved as expected. The patient with insufficiency made a prompt recovery; angina lessened considerably since administration of rauwiloid.

We presently regard the associated problems of coronary insufficiency, or myocardial infarction and persistent hypertension, as an indication for the use of rauwiloid.

*Hypertensive Cardiovascular Disease.* The diagnosis of hypertensive cardiovascular disease was restricted to patients who had left ventricular hypertrophy demonstrated by x-ray or electrocardiogram. Such a complication was found in twenty-six patients prior to therapy. Comparative studies after therapy were available in twenty patients.

Decrease of hypertrophy was noted in ten patients, the status in eight remained the same, while the hypertrophy was more pronounced in two patients.

A decrease in hypertrophy occurred in five of six patients studied in group I, in two of three from group II, and in three of eleven from group III. The two patients with increased hypertrophy were from group III. In one additional patient from group I, and in one from group III evidences of hypertrophy developed while on therapy.

The improvement in hypertrophy occurred in seven of ten white patients and in three of ten Negro patients. Six of the ten white patients were in group I, eight of the ten Negro patients in group III.

Associated coronary artery disease was present in six white patients and one Negro patient. Six patients (five white, one Negro) had a decrease in left ventricular hypertrophy.

Our experience indicates that white patients with enlargement of the left ventricle, and associated coronary disease, did better than Negro patients with an enlarged left ventricle and without coronary artery disease. It is probable that this unusual finding represents a racial

difference in the hypotensive response to the drug.

*Congestive Failure.* Twenty-two patients had congestive failure prior to therapy (thirteen in group I, two in group II and seven in group III). In twenty-one the condition was well controlled with digitalis, diuretics and other customary measures. Control of failure was not made more difficult in any of these patients. One patient in poor control was improved significantly during therapy with rauwiloid. In two patients in group III mild failure developed while on therapy but this was controlled easily with routine measures. Both patients had left ventricular hypertrophy prior to therapy.

There was no indication from this study that congestive failure was affected adversely by either rauwolfia or its alseroxylon fraction. It may be that congestive failure will prove to be easier to regulate in patients on Rauwolfia therapy. A controlled study is presently in progress to determine this point.

*Cerebrovascular Accident (Hypertensive Encephalopathy).* Thirteen patients had experienced a cerebrovascular accident prior to treatment. Improvement in the objective and subjective manifestations of the episode was seen in ten of these patients. One patient in group II experienced a second cerebrovascular accident while on therapy. There was no change in the other two patients. One patient in group III had a fatal subarachnoid hemorrhage; this occurred during the sixty-second week of therapy and was the only fatality during the entire study period.

One patient in group I and two patients in group III had hypertensive encephalopathy prior to therapy. One of the two patients in group III had a recurrence while on therapy.

*Renal Azotemia.* Two patients had chronic renal azotemia prior to therapy. One (Case 13) had advanced chronic glomerulonephritis. Her blood urea nitrogen was elevated persistently (35 to 55 mg. per cent). Total two-hour phenolsulfonphthalein excretion was 6.5 per cent. The urine specific gravity was fixed at 1.012 with a trace of proteinuria. This patient was completely incapacitated, due to general malaise and persistent headaches. She received 10 mg. per day of rauwiloid while under observation for sixty-eight weeks. The average mean arterial pressure (four readings per day) gradually dropped from 133 mm. Hg to 120 mm. Hg. Headaches subsided within a week



and there was progressive improvement in sense of well-being. The patient returned to work within six months. Blood urea nitrogen, which was recorded at weekly intervals remained within the range noted prior to therapy. Repeated urine studies revealed no change.

Although the clinical improvement and the fall of mean arterial pressure are significant, it is perhaps even more noteworthy that despite prolonged treatment with relatively large doses, and an accompanying fall of mean arterial pressure, the kidney status as reflected by the blood urea nitrogen did not deteriorate.

The second patient (Case 11) had a persistent blood urea nitrogen of 25 to 30 mg. per cent prior to therapy. During therapy (2 to 4 mg./day, for fifty-six weeks) there was a fall in average mean arterial pressure from 112 to 98, associated with a slight fall in blood urea nitrogen. This patient also experienced striking relief from persistent headaches.

#### SUMMARY

1. The effect of crude Rauwolfia or its alseroxylon fraction (rauwiloid) was studied in forty patients with hypertension in whom a safe reduction of blood pressure was clinically desirable. Thirty-six had severe associated cerebral, renal or cardiac complications; four were relatively young persons with persistent elevation of the diastolic pressure over a period of years, namely, the type of patient in whom complications are likely to develop.

2. A maintained reduction of more than 10 mm. Hg in the average mean arterial pressure occurred in eighteen (45 per cent) of all the patients, and in 61.5 per cent of the white patients. An average diastolic pressure of less than 90 mm. Hg was obtained in 13 (32.5 per cent) of the patients.

3. The fall of blood pressure in these patients was usually gradual. A single lower reading was often obtained during the first two weeks of therapy; a fall of 10 mm. Hg in the average mean arterial pressure occurred at an average of 4.3 weeks (range two to sixteen weeks) and an average diastolic below 90 mm. Hg at fourteen weeks (range four to thirty-six weeks).

4. The hypotensive response was not influenced by the age or sex of the patient, or by the severity of the hypertension or of the associated complications.

5. There was a significant difference of response between white and Negro patients.

6. Annoying symptoms often observed in patients with hypertension, for example, flushing, throbbing arteries, headaches, anxiety and so forth, were improved in the majority of patients, regardless of the blood pressure response.

7. The complications often associated with hypertension, and which make a safe reduction of blood pressure desirable, are not contraindications to the use of Rauwolfia. Rather, definite improvement of complications was noted in patients with angina, coronary insufficiency, recent myocardial infarction, cerebrovascular accident, hypertensive cardiovascular disease and congestive failure. Two patients with chronic renal azotemia also responded favorably.

8. Sedation, even to the point of apathy, lack of ability to concentrate (particularly in the executive group), nightmares and nasal congestion were the principal undesirable side effects that necessitated a reduction of dosage.

9. Other side effects that bear investigation included transient episodes of peripheral neuritis and a tendency to amenorrhea in younger females.

10. There was no evidence of toxicity, attributable to the drug, upon the hemogram, renal function, liver function, cerebral function or cardiac function.

11. The results suggest that a dose of 6 mg. daily, for twelve weeks, is adequate to determine whether or not a fall in blood pressure will occur with rauwiloid alone. The total daily dose is best administered at bedtime. The eventual maintenance dose may be as low as 1 mg. daily, or less. The best evidence is that 4 mg. daily is the optimal dose.

12. Doses larger than 4 to 6 mg. of alseroxylon may increase the incidence or severity of side actions and are not necessary since larger doses do not increase the hypotensive action.

13. Withdrawal of the drug, or substitution of placebos, results in a gradual rise of the blood pressure and reappearance of undesirable symptoms. Reinstitution of the drug results in a prompt fall of blood pressure associated with symptom changes, and this is considerably more rapid than was the initial response. This indicates that a maintenance dose is necessary.

#### CONCLUSIONS

1. Rauwolfia serpentina derivatives, such as rauwiloid, offer a useful therapeutic approach in patients with hypertension.

2. Approximately half of the patients with



complicated hypertension and persistently elevated diastolic pressures responded favorably, both subjectively and objectively. Good subjective improvement was seen in virtually every case whether or not a hypotensive response was obtained.

3. Ease of administration and the absence of dangerous side effects or toxic reactions are important advantages to both physician and patient.

4. Unpleasant side effects are seen occasionally. These are usually relieved by dosage reduction.

5. Unfavorable effects on the cardiovascular system or cerebral, renal, hepatic or blood functions were not observed.

6. The results indicate that Rauwolfia compounds such as rauwiloid are effective when given alone in a large percentage of patients provided that they are used for an adequate period. In cases in which a satisfactory hypotensive response is not obtained the addition of other safe hypotensive agents is indicated.

7. The significant difference in response between white and Negro patients indicates that this racial factor should be considered in any study of hypotensive agents.

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# Therapeutic Activity of Desiccated Thyroid Substance, Sodium L-Thyroxine and D,L-Triiodothyronine\*

## *A Comparative Study*

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THE development of a commercially practical method for synthesizing thyroxine,<sup>1</sup> the identification of 3,5,3'-L-triiodothyronine in human plasma<sup>2</sup> and the recognition of its physiologic importance<sup>3,4</sup> have stimulated considerable interest in the re-evaluation of thyroid hormone therapy. Several reports have already appeared describing the oral or intravenous use of sodium L-thyroxine,<sup>5-17</sup> L-triiodothyronine<sup>11-13,16-20</sup> and D,L-triiodothyronine<sup>16,17</sup> in patients with myxedema. That desiccated thyroid substance, thyroxine and triiodothyronine are all hormonally active in such trials is universally agreed. However, reported investigations with the best human test subject, the myxedematous patient, are not yet of sufficient number to settle completely the relative intensity, speed and duration of action, as well as the variations in responsiveness. The present report deals with experiences with twelve patients suffering from adult myxedema. The manner of approach differs in one respect from most if not all of the other studies of human subjects. In the present work, following attainment of a euthyroid state under therapy, the patient has been allowed to lapse into a measurable degree of hypothyroidism prior to the beginning of therapy with the same or a second thyroid preparation. This has afforded us repeated comparisons under conditions as nearly identical as possible for us to achieve.

### METHODS

One man, thirty-seven years old, and eleven women, ranging in age from thirty-four to sixty-five with an

average age of fifty-three and a half years, were the subjects of this study. Each had the classical symptoms and signs of myxedema. The diagnosis was further confirmed by determination of the basal metabolic rate, serum cholesterol and, in some instances, the serum protein-bound iodine, thyroidal uptake of radioactive iodine and the twenty-four hour excretion of creatine of a person on a meat-free diet. Manifestations of myxedema had been present for periods varying from six months to twelve years prior to recognition, with an average duration of 3.7 years. In seven subjects the development of myxedema was spontaneous; in three it followed thyroidectomy; in one radiation therapy, and in the remaining one the prolonged use of an antithyroid compound. The initial basal metabolic rates of the group ranged from minus 16 to minus 47 per cent, with an average of minus 34.9 per cent. Serum cholesterol values, performed by the method of Pearson, Stern and McGavack,<sup>23</sup> varied from 291 to 443 mg. per 100 cc. with an average of 358.4 mg. per 100 cc. The serum protein-bound iodine, carried out by the method of O'Neal and Simms<sup>24</sup> was initially 3.9  $\mu$ g. per 100 cc. or less. Because of the changes initially present, serial determinations were made throughout the study, as well as repeated estimations of the urinary 17-ketosteroids, blood counts, electrocardiograms and cardiac roentgenograms.

Initially, each subject was brought to a euthyroid state by the use of one of the three preparations to be compared. Desiccated thyroid was thus employed in three subjects, sodium L-thyroxine in seven and D,L-triiodothyronine in two. Following such preparation, which was designed for as valid subsequent comparison as possible, each subject was allowed to revert to a definitely hypothyroid state, as shown by increasing weight and cholesterol, a return of definitive subjective symptoms and a significantly falling basal metabolic rate and urinary 17-ketosteroid excretion. Before

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TABLE I  
COMPARISON OF ACTIVITIES OF DESICCATED THYROID SUBSTANCE, SODIUM L-THYROXINE AND  
D,L-TRIIODOTHYRONINE IN TWELVE CASES OF ADULT MYXEDEMA

Material	Trials	Daily "Optimal" Dose*		Control (days)		Relapse (days)	
		Range	Average	Range	Average	Range	Average
Desiccated thyroid.....	15	120-210	152.6	14-35	21.0	28-42	31.7
Sodium L-thyroxine.....	19	200-350	258.0	12-35	19.2	21-42	26.4
D,L-Triiodothyronine.....	26	100-175	145.1	4-10	5.0	5-13	9.8

\* In milligrams for desiccated thyroid, in micrograms for the other two materials.

beginning any period of trial the basal metabolic rate was allowed to drop to minus 20 per cent or below, the twenty-four hour urinary 17 ketosteroid excretion to 6.0 mg. or below and the serum cholesterol to rise above 300 mg. per 100 cc.

Six of the women were confined to the hospital throughout the study; the remainder were followed as outpatients.

In patients prepared as described, each of the three preparations\* was tested at several levels of dosage to ascertain (1) the optimal daily dose, (2) the speed with which control was achieved, (3) the rapidity with which manifestations returned following the use of each of the drugs used, and (4) the nature and intensity of any side or untoward effects. The daily dosage used varied for desiccated thyroid from 30 to 210 mg. (one-half to three gr.), for sodium L-thyroxine from 50 to 350  $\mu$ g., and for D,L-triiodothyronine from 25 to 200  $\mu$ g. In each instance this was always given as a single dose for desiccated thyroid; in two or three equally divided doses for sodium L-thyroxine and triiodothyronine when the daily amounts were more than 100  $\mu$ g. and 50 mg., respectively, but in one dose when the amounts were below this level. By these methods a total of sixty trials were made in the twelve subjects at levels of dosage which satisfactorily restored the subjects to a euthyroid state. All estimates of the time and comparative dosages are in relation to such optimal or "near-optimal" amounts of drug.

#### RESULTS

It will be seen from Table I that fifteen trials were made with desiccated thyroid, nineteen

\* Supplies of desiccated thyroid, U.S.P. strength, were made available through the courtesy of Dr. E. A. Sharp of Parke, Davis and Co.; of sodium L-thyroxine, under the trade name synthroid, through the courtesy of Dr. Robert P. Herwick of Baxter Laboratories, and of D,L-triiodothyronine through the courtesy of Dr. Elmer Severinghaus of Hoffmann-La Roche, Inc.

with sodium L-thyroxine and twenty-six with D,L-triiodothyronine. Approximately three years were needed for the completion of the study. Only one subject was continuously observed during that time, two participated for from two to three years, five from one to two years, and five from six to twelve months.

The average daily control dose for desiccated thyroid was 152.6 mg. with a range of from 120 to 210 mg.; that for sodium L-thyroxine was 258.0  $\mu$ g. with a range from 200 to 350  $\mu$ g., and that for D,L-triiodothyronine was 145.1  $\mu$ g. with a range from 100 to 175  $\mu$ g. (Table I.)

The number of days necessary to bring the subjects back to a euthyroid state with optimal doses of the respective drugs was, for desiccated thyroid 21.0, for sodium L-thyroxine 19.2 and for D,L-triiodothyronine 5.0, with individual variations of time as noted in Table I. The number of days necessary for the patients to relapse into a myxedematous state, fulfilling the criteria mentioned under "methods of procedure," was: for desiccated thyroid 31.7, for sodium L-thyroxine 26.4, and for D,L-triiodothyronine 9.8, with individual fluctuations as recorded in Table I.

Fluctuations for cholesterol strikingly paralleled the values for the basal metabolic rate and were most informative during the trials with triiodothyronine, in which the rise and fall occurred simultaneously with (but in inverse ratio to) alterations in the basal metabolic rate. With the other two preparations, the cholesterol values lagged slightly behind those for the variations in basal metabolism.

While the urinary excretion of 17-ketosteroids was always low when the subject was myxedematous and within normal range in a reason-



able time after restitution of the euthyroid state, the values did not accurately mirror the degree of improvement or relapse.

Ten of our subjects had frank secondary anemia at the outset, while the other two showed red blood counts within the low normal range. The increase in these counts with the establishment of the euthyroid state ranged from 0.7 to 1.9 million per cu. mm. Variations in these counts in relation to relapse and retreatment occurred but were of no value in following the progress of the patient.

All subjects lost from 1 to 5 kg. of weight and showed an increase in pulse rate while using any one of the three preparations in dosages sufficient to achieve a euthyroid state; these changes rather accurately reflected the condition of the patient, although lagging somewhat behind the more useful criteria already mentioned. Subjective symptoms varied from patient to patient. In each instance those most sensitive to any change in the status of thyroid function were employed to aid us in appraising the overall picture.

Unless doses of the thyroid preparations necessary to maintain a euthyroid condition were exceeded, the only side effects noted were concerned with cardiac function. Angina was most frequently observed and was most troublesome in connection with the administration of triiodothyronine. In one patient this drug was tried on five different occasions and even after a euthyroid state was obtained its discontinuance was necessary. Later this patient was very slowly stabilized by the use of desiccated thyroid substance.

#### COMMENTS

*Dosage Equivalents.* From the data presented it appears that in the treatment of myxedema 60 mg. or 1 gr. of desiccated thyroid substance is about equivalent to 100  $\mu$ g. of sodium L-thyroxine and to approximately 60  $\mu$ g. of D,L-triiodothyronine. The results of Selenkow and Asper<sup>16</sup> are in rather close accord, as they found 200  $\mu$ g. of D,L-triiodothyronine equivalent to 300  $\mu$ g. of sodium L-thyroxine in the control of myxedema. Frawley and his associates<sup>18</sup> believe that D,L-triiodothyronine is proportionately more active than sodium L-thyroxine and found euthyroidism to be achieved in their myxedematous subjects with average doses of 150 mg. of desiccated thyroid, 400  $\mu$ g. of sodium L-thyroxine or 200  $\mu$ g. of D,L-triiodothyronine. These are the only reports which have come to our attention

in which D,L-triiodothyronine has been used in human subjects.

*Time Necessary for Control of Myxedematous State.* Calorigenic responses to triiodothyronine have been observed six hours following intravenous injection<sup>21,22</sup> and within twenty-four to forty-eight hours after oral administration.<sup>14,16,17</sup>

The periods mentioned in Table I refer to the time necessary for the patient to reach a euthyroid state under the specific conditions of these tests. Some changes could be noted within forty-eight hours in all subjects when triiodothyronine was used, while from five to ten days were required to observe any change following administration of desiccated thyroid or sodium L-thyroxine. No significant difference was noted in the number of days required to produce euthyroidism by desiccated thyroid and sodium L-thyroxine but the period for triiodothyronine was strikingly shorter. Several workers<sup>14,16,17,21,22,24</sup> believe this is due to the fact that triiodothyronine is in the form in which tissue cells actually use thyroid hormone. An abundance of data in the literature support this view.

*Time Necessary for Relapse from Euthyroidism Following Cessation of Therapy.* The intervals for relapse to the myxedematous state following cessation of desiccated thyroid and sodium L-thyroxine are not materially different, but for triiodothyronine the period is relatively short. This is in accord with the fact that the latter materially is rapidly absorbed and rapidly used by the tissues.<sup>24</sup>

*Side Effects.* It seems likely that the cardiac symptoms caused more readily by triiodothyronine than by desiccated thyroid or sodium L-thyroxine when used in equivalent doses are due to the more rapid action of the former in the tissues and the inability of metabolic factors in the cardiac musculature to compensate for this rapidly imposed additional load. At least such an interpretation is in accord with the suggestions of other investigators.<sup>14,16-18</sup>

#### SUMMARY AND CONCLUSIONS

In twelve subjects with myxedema, fifteen studies were made with desiccated thyroid, nineteen with sodium L-thyroxine and twenty-six with D,L-triiodothyronine, all given in dosages of sufficient magnitude to produce an euthyroid state in a minimum of time.

It was found that the average daily optimal dose of desiccated thyroid varies from 120 to

180 mg., that for sodium L-thyroxine from 200 to 350  $\mu$ g., and that for D,L-triiodothyronine from 100 to 175  $\mu$ g. It is concluded that 60 mg. of desiccated thyroid are equivalent in activity to about 100  $\mu$ g. of sodium L-thyroxine and to 60  $\mu$ g. of D,L-triiodothyronine.

In the control of human myxedema, D,L-triiodothyronine produced the euthyroid state in about one-fourth the time required by desiccated thyroid substance or sodium L-thyroxine. Relapse upon discontinuance of therapy was most rapid following the use of D,L-triiodothyronine and about equally long for desiccated thyroid substance and sodium L-thyroxine.

Angina pectoris was a more troublesome side effect in connection with the administration of triiodothyronine than with either of the other materials, presumably because of its more rapid action. Consequently, use of triiodothyronine requires more frequent observation of the patient to avoid untoward side effects.

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# Seminar on Allergy

## Bronchial Asthma\*

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**D**ISCUSSION of asthma today imposes a double task involving two entirely unrelated subjects of medical interest, namely a branch of immunology of great clinical importance and the disturbances in respiration and pulmonary hemodynamics. This last has been a rapidly expanding field because of the increasing tendency in recent years to apply principles of pulmonary physiology and tests of pulmonary function in clinical medicine and because diffuse obstruction of the airway is the most striking and probably the most common readily recognizable abnormality of pulmonary function in non-infectious pulmonary disease.

Asthma has been well described in many texts and a formal description of the disease will not be attempted. Likewise a discussion of possible endocrinologic and psychologic factors will be omitted.

As some of the terms to be used do not have the same meaning for everyone, it seems imperative to describe their usage here in some detail. "Asthma" may be regarded as a form of diffuse bronchial obstruction characterized by a high degree of reversibility. It is not assumed here that an allergic reaction is involved in its pathogenesis. Obstructive pulmonary disease which is not reversible is usually called "emphysema" and the word will be used in this sense here. An irreversible increase in residual volume, unassociated with the disturbances of anatomic structure so characteristic of emphysema, also occurs and is usually referred to as hyperinflation. Complete irreversibility, hyperinflation and emphysema appear, clinically, to constitute a continuous spectrum. Nevertheless, asthma is considered to be an obstructive disease of the airway whereas emphysema, although exhibiting striking obstructive manifestations, is usually considered to be a disease of the pulmonary parenchyma characterized by degenera-

tion of elastic tissue.<sup>1</sup> However, a second view holds that emphysema is an inflammatory lesion of the airway leading to obstruction of the terminal portions.<sup>2</sup> It has also been suggested that, even aside from the pneumoconioses, the disease is caused in many instances by inhalation of irritating particles (or gases ?) of which tobacco smoke appears to be the most important.<sup>3-5</sup> The relationship between asthma and emphysema, and the possible role of particle size in determining the location of the lesion has been discussed from this standpoint.<sup>5</sup> Viewed in this way, the pathogenesis of asthma and emphysema has important similarities and clinically the features of the two conditions overlap so strikingly as to make it impossible to draw a line between them. Most of the studies on obstructive disease have been made in emphysema. However, all the abnormalities of ventilation which have been described in emphysema are also demonstrable in asthma.

In addition to the words asthma, hyperinflation and emphysema, the meaning assigned here to status asthmaticus and allergy should be given. "Status asthmaticus" indicates a severe and persistent form of asthma unrelieved by ordinary therapeutic agents. Patients dying under these circumstances have, as the striking and probably the lethal lesion, widespread obstruction of the bronchial tree, including the smaller bronchi (and therefore out of reach of the bronchoscope), by an elastic form of mucus. This, in association with the probable increase in tone of the smooth muscle in the wall of the bronchi and edema of the mucosa, is entirely adequate to explain the extreme degree of respiratory embarrassment. Recovery from a severe asthmatic attack is often accompanied by expectoration of copious amounts of sticky mucus indicating that the mucus seen at autopsy is often present in severe asthma during life.

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If present, the obstructing mucus will thwart efforts to relieve asthma with bronchodilators, which however will become effective again when the mucus is dislodged. This may account for the claim that aminophylline has a specific action in the restoration of responsiveness to the bronchodilator action of epinephrine.

The words "allergy" and "allergic" will be used here to mean an acquired specific alteration in the capacity to react, mediated by the interaction between antigen and antibody. Used in this restricted sense, the word "allergic" would be applicable to the group of conditions including rhinitis, asthma, eczema and hives, often jointly referred to as atopy (a useful term), only if an antigen-antibody reaction were a *sine qua non*. This, however, cannot be accepted at present as there are many instances of the four conditions cited wherein one is unable to discover satisfactory evidence for an antigen-antibody reaction as a cause of the clinical manifestations. The advantage in limiting the meaning of the word allergy in this fashion is, therefore, that one avoids the embarrassment of having to classify as allergic such instances of the aforementioned four diseases as may exhibit no recognizable allergic reaction to account for their presence.

#### FACTORS AFFECTING RESISTANCE TO AIRFLOW IN BRONCHIAL TREE

No organ is more clearly a "life-line" than the bronchial tree. When its anatomy is finally correlated in detail with the functions it serves, we shall probably find that it is no simple conduit for air but rather precisely designed to minimize turbulence and the effects of gaseous viscosity and thus to spare muscular effort in the all-important act of ventilation. If the airway is indeed "engineered" as carefully as many other organs are known to be, then relatively trivial changes in the caliber at one point as compared with another or roughness on the mucosal surface might well have dire consequences. This possibility may help to explain the extremes of disability to which the asthmatic patient is subject.

In general, resistance to airflow in the airways of larger caliber will depend on the amount of turbulence which accompanies flow. In the smaller airways, on the other hand, turbulence does not occur or is of less importance and viscosity of the gas becomes dominant as a factor in resistance. Turbulence unquestionably is a striking accompaniment of asthma and accounts

for the wheezes which are so characteristic. However, with narrowing of the airway, if it reaches the point where turbulence is lessened and viscosity becomes more important, airflow will be less noisy although the obstruction is greater. Furthermore, in the presence of a given degree of bronchial obstruction, the auscultatory signs will become more intense with an increase in minute volume and will decrease when this becomes less (*v. seq.*). It is for these reasons chiefly that the intensity of auscultatory signs cannot be relied upon as a measure of the degree of obstruction and measurement of air flow is necessary.

*Factors Influencing Patency of Airway.* The patency of the airway will depend on: (1) the degree of expansion or collapse of the lung; (2) narrowing of the airway by contraction of smooth muscle or by fibrosis in the wall of the bronchial tree; and (3) encroachment on the airway arising from swelling or thickening of the bronchial walls by edema or inflammation.

*Degree of Expansion or Collapse of Lung.* This point has received little attention by those interested in bronchial asthma. When normal adults inspire maximally and then expire forcibly and as completely as possible into an apparatus which records the rate of expiration, the rate of expiration decreases in a regular manner until almost the entire volume is expired and flow drops to a very low level.<sup>6</sup> The rates of flow obtained in this manner are reproducible on successive occasions within narrow limits. In other words, resistance to expiration increases progressively and in a predictable fashion during expiration. This rising resistance is probably very largely a result of narrowing of the airway as expiration progresses. However, airflow ceases even though air remains in the lung (residual volume) because of the rigidity of the thoracic cage and some of the decrease in the rate of expiration occurring as this point is approached may be attributable to the increasing resistance offered by factors other than resistance to air flow. In the presence of asthma (and emphysema), however, expiration apparently comes to an end because the airway closes off as the lung becomes smaller. (Fig. 1.)

*Narrowing of Airway by Contraction of Smooth Muscle or by Fibrosis.* Contraction of smooth muscle in the bronchial wall has received a great deal of attention and is believed to play an important and perhaps determining part in the acute asthmatic attack. (*v. seq.*). As already

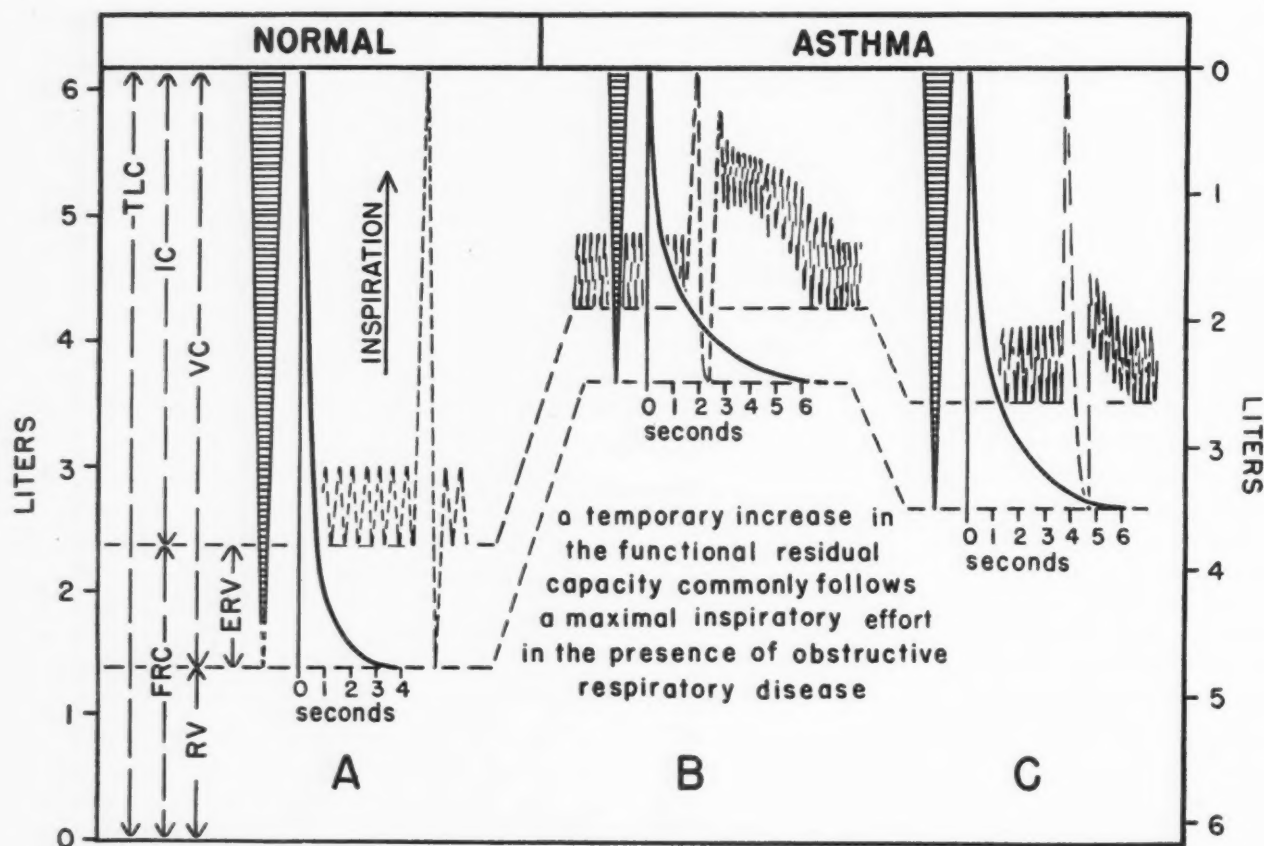


FIG. 1. Schematic representation of some of the changes in the lung which accompany asthma. The following abbreviations are used in the illustration: TLC, total lung capacity; IC, inspiratory capacity; FRC, functional residual capacity; VC, vital capacity; RV, residual volume; ERV, expiratory reserve volume. The scale at the extreme left indicates the volume of air within the lung; that at the extreme right indicates the volume which has left the lung measured from the point of maximal inspiration. A, at the extreme left subdivisions of lung volume are shown which are appropriate for a normal young man six feet in height. A tracing obtained by conventional spirometry with the patient breathing in a closed system is represented by the broken line. The heavy solid line descending from above downward in a curve represents an expirogram,<sup>10a</sup> a tracing obtained on a rapidly moving kymograph (1 cm./sec.) during performance of the vital capacity in the usual manner. The converging lines enclosing a cross-hatched area represent the caliber of the airway leading from the air spaces within the lung at various levels of chest expansion. Expiration is probably not brought to an end by closure of the airway in normal young adults. B, a spirometric tracing, an expirogram and the caliber of the airway are shown as they might appear during an attack of asthma in a person of the same height and age as that described in A. Abnormalities of the degree shown are not unusual although they will be associated with marked symptoms and signs. Among the means of measuring the changes in pulmonary function which occur during asthma, one of the most characteristic, informative and easily measured is the expirogram. There is little question that in asthma a maximal expiratory effort is brought to an end by closing off the airway. C, administration of a bronchodilator drug to a patient with findings as shown in B might well bring about this pattern. A patient with this degree of abnormality might be free of respiratory discomfort and have few physical signs; nevertheless vigorous therapy might still induce striking improvement in function.

mentioned, changes of caliber are to be expected during inspiration and expiration and such changes are probably not mediated by smooth muscle. It is therefore not justifiable to conclude that an observed narrowing is necessarily caused by spasm. At present, there is no direct evidence in man for bronchospasm as the cause of, or the principle factor in, the development of an asthmatic attack. For this reason the words "bronchospasm" and "bronchoconstriction" should not be used synonymously with obstruction.

*Encroachment on Airway.* Inflammation may occur in any tissue and as it is accompanied by vascular engorgement, edema, infiltration of leukocytes and proliferation of fibroblasts, the end result is an increase in the bulk of the tissue involved. When this occurs in the wall of the bronchial tree, some encroachment on the lumen is to be expected with consequent narrowing of the airway.

Any change in the lung which results in a temporary or permanent reduction in the

caliber of the airway will greatly augment the effect on resistance to airflow which further narrowing will have. Imagine that a bronchiole 0.5 mm. in radius undergoes a decrease in radius of 0.1 mm. The cross sectional area will change from 0.79 mm.<sup>2</sup> to 0.50 mm.<sup>2</sup>, a reduction of 36 per cent. Now consider the same bronchiole narrowed by disease to 0.3 mm. radius and then subjected to a decrease in radius of 0.1 mm. as before. The cross sectional area will now change from 0.28 mm.<sup>2</sup> to 0.13 mm.<sup>2</sup>, a decrease of 53 per cent. A patient with an already narrowed airway, therefore, is far more vulnerable when exposed to any agent which may cause further narrowing of the airway.

#### PULMONARY FUNCTION IN ASTHMA

Pulmonary function in asthma has been recently reviewed<sup>7</sup> and an excellent text on clinical physiology of the lung and tests of pulmonary function is available.<sup>8</sup> Therefore a full description of the methods and principles of tests of pulmonary function in asthma is unnecessary here.

Some of the changes which occur in asthma are depicted schematically in Figure 1 which also shows the lung volumes, conventional spirographic tracings made in a closed system, expiratory tracings made during performance of the vital capacity and an indication of the change in the caliber of the airway which probably occurs under the conditions depicted. Clinically recognizable asthma is accompanied by changes so gross that the simplest apparatus will readily detect them.

With certain rather unimportant exceptions, asthma is accompanied by a reduction in the vital capacity, the degree of which correlates well with the severity of the disease. For this reason the vital capacity alone is a useful measurement in asthma. As there is no reason to suppose that the total lung capacity changes during an asthmatic attack, an observed reduction in vital capacity is, by definition, a measure of the increase in the residual volume. The vital capacity is more useful on any given occasion when compared with a normal or "predicted" value based on standards for age, sex and height.<sup>9</sup> This measurement is even more useful clinically when compared to values obtained in the same patient at a time when he is entirely free of asthma or as well as he can become under the most vigorous therapy.

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The inspiratory capacity and the expiratory reserve volume are likewise reduced in asthma, sometimes the one relatively more so than the other. Their values, absolute and relative, are probably determined by the need to open the airway sufficiently to permit relatively effortless tidal ventilation. If the minute volume increases, a tracing of tidal ventilation will usually shift in the direction of inspiration and, if this occurs without an increase in residual volume, the expiratory reserve volume will increase at the expense of the inspiratory capacity. Measurement of the inspiratory capacity and the expiratory reserve volume are useful as a means of indicating the level of chest expansion selected by the patient for tidal ventilation in relation to the point of maximal expiration and maximal inspiration. Tidal ventilation with the chest in an expanded position must be carried on with continuous muscular force to counteract the elastic recoil of the chest wall and this fact diminishes the advantage gained by opening the airway.

The residual volume is increased in asthma, often markedly so and always at the expense of the vital capacity. It is a measurement which need not often be made in asthma. However, it should be remembered that the vital capacity may be reduced for a number of reasons (space-occupying masses or air within the chest, muscle weakness, stiffness or rigidity of the thoracic cage and intrathoracic structures) and therefore measurement of the residual volume is often helpful.

Even more striking than the changes in the subdivisions of the pulmonary volume is the reduction in the speed of airflow, especially during expiration. The expiratory flow rate is strikingly independent of the degree of effort, that is to say, the maximum expiratory rate is reached with relatively little effort and no increase in the force with which expiration is made will cause the expiratory flow-rate to exceed this maximum. Measurement of this rate is extremely valuable as an indication of the obstructive defect in asthma in particular, and in clinical medicine in general, and can be easily done<sup>10</sup> with a spirometer and kymograph moving at 1 cm./sec. During the exacerbations and remissions of the disease the maximal expiratory rate fluctuates between very wide limits and can be used as a sensitive index of changes in the intensity of the disease. The maximum breathing capacity is the usual pro-



cedure for measurement of resistance to airflow. However, this test has a number of disadvantages<sup>7</sup> and is unsuitable in asthma.

Returning once more to the vital capacity, the circumstances under which this measurement is made must be described if it is to have any exact meaning in obstructive disease. Characteristically in emphysema and often in asthma, the volume expired in a single maximal expiratory effort (vital capacity) will be greater if expiration is made slowly than if made with maximal expiratory force, and this difference may be large.<sup>7,11</sup> As already mentioned some degree of narrowing or passive collapse of the bronchial tree occurs in expiration even in the normal lung. In the already narrowed airway this will have a relatively greater effect on expiratory airflow. There is abundant evidence (to be reviewed subsequently) that in asthma as well as in emphysema the degree of narrowing in the various branches of the airway is not uniform and that this leads to non-uniform ventilation of the respiratory units. With maximal inspiration, spaces within the lung which ordinarily contribute little to gas exchange will be opened and filled. However, on forced expiration the well ventilated areas will empty first and the decrease in the caliber of the airway which accompanies this emptying of the lung will cause those areas which are poorly ventilated to become shut off. No amount of expiratory effort will be successful in forcing the air out and the volume expired will be accordingly decreased. If, on the other hand, a voluntary effort is made to expire slowly and without force, some of these areas may empty along with the better ventilated areas and the vital capacity will be accordingly larger. The air trapped in the lung in performance of the vital capacity made with maximal expiratory effort is slowly expired during a number of cycles of quiet respiration. Its presence has the effect of increasing the residual volume and, in spiographic tracings made in a closed system, a temporary shift of the tracing in the direction of inspiration as depicted in Figure 1B and C is common in asthma as well as in emphysema.

The nitrogen washout method, the helium (or hydrogen) dilution method or the single breath technic using the nitrogen meter are applicable to measurement of the degree to which the distribution of the inspired gas is rendered non-homogeneous in asthma. This disturbance in asthma seems to be similar to that seen in emphysema except that it is

reversible wholly or in large part. Evidence for the presence of this abnormality can be elicited, as already mentioned, by the difference in the vital capacity done with and without maximal expiratory force and also by careful analysis of the changing slope of the curve obtained when a tracing is made during performance of the vital capacity.<sup>6</sup>

Non-uniform distribution of inspired gas among the respiratory units of the lung, or "mixing" defect, detracts from pulmonary efficiency. If the defect is pronounced, a significant fall in the arterial saturation of the blood and a rise in the arterial  $p\text{CO}_2$  ensue, apparently limited or prevented in many instances of asthma by a compensatory increase in ventilation. The increase in ventilation occurs in the face of bronchial obstruction and the chest will be held in an expanded position, both achieved with the expenditure of muscular work. This increased work requires its share of oxygen and contributes its own increment in  $\text{CO}_2$ . Thus the net gain in oxygen acquired and  $\text{CO}_2$  excreted will be less than would otherwise be expected with the compensatory rise in ventilation. Unfortunately, it will be not only because of the increased work which obstruction imposes that the higher level of ventilation will be relatively unrewarding but also because of the "mixing" defect already mentioned. Thus the patient with an asthmatic attack must work harder with less efficient equipment.

As in advanced chronic obstructive emphysema, but fortunately less commonly, in patients with severe asthma, especially if this is of more than a few days' duration, respiratory acidosis may develop<sup>12</sup> which, associated as it is with an elevated concentration of  $\text{CO}_2$  in the alveolar air, permits excretion of  $\text{CO}_2$  at a ventilatory level below what would otherwise be required. In this sense the development of respiratory acidosis may be regarded as compensatory. However, such a view of the matter is not offered as reassurance because respiratory acidosis is evidence of grave respiratory embarrassment and is accompanied by a significant degree of hypoxia. This last often leads to the administration of high concentrations of oxygen which will almost invariably relieve the hypoxia but at the bedside one may be unable to appreciate the fall in ventilation which oxygen also brings about, apparently by lessening the hypoxic respiratory drive upon which the already depressed level of ventilation seems to depend. The danger of

aggravating respiratory acidosis in this manner has been repeatedly pointed out.

Diffusely distributed obstruction of the airway and impairment of the distribution of the inspired gas are of sufficient magnitude to explain fully the respiratory embarrassment characterizing an asthmatic attack. Evidence is lacking that asthma is also accompanied by a decrease in the permeability of the alveolar-capillary membrane to  $O_2$  and  $CO_2$ .

#### THE INDUCED ASTHMATIC ATTACK

Patients with bronchial asthma will almost invariably suffer an abrupt reduction in vital capacity and a slowing of the respiratory rate often accompanied by frank wheezing if they are given histamine.<sup>13-15</sup> The dose which will bring this about in asthmatic subjects produces no change in vital capacity or speed of expiration in non-asthmatic subjects with normal lungs. The drug may be given by intravenous injection of 0.02 to 0.06 mg. or by inhalation from a nebulizer. Such induced asthmatic attacks occur promptly; they appear to have the characteristics of spontaneous asthma and are readily relieved by administration of a bronchodilator. As attacks may be induced in asthmatic subjects who are entirely free from symptoms and who appear to have a normal airway as judged by the rate of airflow on forced expiration, histamine must produce a very substantial change. It would seem logical, therefore, to attribute the attack induced by histamine to contraction of smooth muscle rather than to edema or engorgement of the bronchial wall but direct evidence on this point is lacking.

The patient with emphysema will react in a similar way. However, as the airway in such patients is already markedly narrowed, a very slight decrease in caliber, such as might arise from an amount of smooth muscle spasm or edema which histamine would be expected to induce in a normal airway, would be sufficient to bring about striking manifestations of obstruction. There is some justification in attributing the reactivity of the asthmatic lung to histamine to a different mechanism from that which is present in emphysema and to regard the first as a "specific" responsiveness. However, we have here once more a striking similarity between asthma and emphysema, the significance of which awaits investigation.

Acetylcholine will likewise induce asthmatic attacks in asthmatic individuals. It is convenient

in practice to use acetyl- $\beta$ -methylcholine for this purpose. This drug when given parenterally is somewhat more active than histamine<sup>14</sup> as judged by the ratio of the dose causing asthma to the largest dose which may be given to normal persons without causing disagreeable systemic effects. It is of some interest that asthmatic subjects are no more prone to develop systemic manifestations following the parenteral administration of histamine or acetyl- $\beta$ -methylcholine than are normal subjects and attacks of rhinitis and urticaria are not induced.

Recently, serotonin (5-hydroxy tryptamine) has been reported to cause asthmatic attacks when given to asthmatic subjects,<sup>16</sup> much as histamine does. Limited experience<sup>17</sup> again indicates that asthmatic subjects are no more susceptible to the systemic effects of intravenously injected serotonin than are normal subjects and that the drug is active in producing asthma only when given by inhalation.

Sympathomimetic drugs and aminophylline are effective in preventing or relieving asthma induced by these three agents. The antihistaminic drugs are very active here against the pulmonary effects of histamines, as is atropine against those of acetyl- $\beta$ -methylcholine, although the specificity is not absolute.

In properly selected patients with asthma, inhalation of an aerosolized extract of the appropriate allergen will be followed by asthma.<sup>18</sup> The interval between exposure and the height of the reaction is several minutes (usually five or six) and attacks induced in this manner, although readily controlled, are less easily relieved completely and promptly with bronchodilator drugs than are those induced by the three agents mentioned.

#### ALLERGY AND ASTHMA

As a group, patients with asthma share with those whose hereditary background includes asthma, hay fever, infantile eczema and hives a tendency to acquire skin-sensitivity to one or more substances, especially when inhaled but also occasionally when ingested. Among those who develop skin-sensitivity to one or more allergens, some on exposure develop asthma, rhinitis, dermatitis (in the opinion of some) and occasionally hives. In perhaps one-third of patients with asthma, attacks seem to occur only as a direct result of exposure to one or more of these substances. Among this last group pollens are by far the most common cause of symptoms



so far as one can determine at present. As pollens have a seasonal occurrence, correlation between exposure and the development of asthma is made with ease. On the other hand, allergens so ubiquitous that we all suffer daily exposure to them throughout the year are difficult to assess as causes of symptoms. Furthermore, symptoms do not always follow immediately upon exposure and, as asthma tends to be worse at night irrespective of the cause if exposure is continuous, a relationship between exposure and the occurrence of symptoms may not be evident. House dust illustrates this well, as may even the dander of animal pets. In this connection the common failure of patients to recognize their dog or cat as the cause of symptoms is surprising in view of the common knowledge that animal pets are a frequent cause of asthma. It is rash to conclude, therefore, that the failure to see a causal relationship between exposure to certain substances and the development of symptoms is adequate as a basis for excluding such a relationship. Another approach may be necessary. For example, convincing evidence that house dust, the allergenically active component(s) of which remain unidentified, is an important cause of asthma rest on: (1) a strong clinical impression that this is the case; (2) the capacity of suitable aqueous extracts to react in the skin in a manner which is characteristically allergic<sup>19</sup> (such reactions are not a result of non-specific irritation); and (3) the ease with which asthmatic attacks are induced on exposure to house dust extracts by inhalation in selected asthmatic patients.<sup>20</sup> Indeed, based on the evidence available, this allergen seems to lead all other airborne agents in importance, including ragweed pollen.

Those asthmatic patients in whom asthma develops on exposure to an allergen, such as ragweed pollen, invariably (or almost invariably—there is disagreement on this point) have a marked degree of skin-sensitivity to injected ragweed pollen extract. The blood of such patients contains an antibody which can be demonstrated only by its capacity to confer specific reactivity to normal skin. For this reason it is usually referred to as the "skin-sensitizing antibody." This antibody appears to be responsible for the pulmonary response (asthma) which occurs when the allergen is inhaled. Treatment of the patient with injections of allergenic extract does not significantly alter the amount of this antibody. Such treatment does, however, induce the formation of a new antibody having

entirely different characteristics among which is the capacity to combine preferentially with the allergen and thus apparently prevent it from reacting with the skin-sensitizing antibody. This new antibody is usually called "neutralizing antibody" and is credited by some<sup>21,22</sup> but not by others<sup>23-25</sup> with the benefits which follow injection therapy. This antibody possesses attributes which would be expected to afford protection from allergens. In the writer's opinion, this fact should be given more weight than a correlation between titers of an antibody which is difficult to quantitate and clinical results which are influenced by many uncontrollable variables.

*Relationship between Reactivity of Bronchial Tree and Allergy.* There is some advantage in considering the tendency to the development of asthma, whatever the cause, apart from the allergic factor or factors which are frequently so conspicuously associated with asthma.

In a study of patients with asthma it was found that, in general, those with the severest asthma were also those who reacted most intensely to intravenously injected histamine.<sup>14</sup> If the severity of the disease is a factor in determining whether or not a given dose of histamine will cause an attack, then severity may also play a part in determining whether or not a patient will have significant aggravation of symptoms following a variety of stimuli: respiratory infections; inhalation of irritating dusts, fumes or gases; exercise; emotional upsets; and so on. The common denominator among these seems to "trigger" an already hyperirritable bronchial tree. For each degree of susceptibility to these "non-specific" causes of asthma, arbitrarily assigned values ranging from 0 to + + +, one can, by history, skin tests and inhalation tests done with suitable allergens, designate the degree of allergy present by assigning values for this, again ranging from 0 to + + +. They can then be arranged as shown in Table 1.<sup>26</sup> "Extrinsic" asthma<sup>27</sup> (asthma caused only by allergens) is then represented by the presence of a low degree of non-specific pulmonary reactivity and a high degree of allergy and symptoms occur only upon inhalation of the appropriate allergen or allergens. Exposure to an allergen is regarded here as a sufficiently intense stimulus to induce asthma even when the reactivity of the bronchial tree is of a low order. "Intrinsic" asthma would be represented in Table 1 by + + + reactivity to non-specific



factors and the absence of allergy. A large number of patients with asthma will come between these two extremes. As a multiplicity of factors can stimulate the development of asthma in these two categories, symptoms will tend to occur throughout the year and control of recognizable allergic factors may still leave the inherent reactivity of the bronchial tree unchanged and cannot, therefore, be expected to give complete relief. The nature of this reactivity is unknown. It is markedly lessened, but not abolished, by ACTH and cortisone and it seems to wax or wane unpredictably and perhaps spontaneously in the course of time. This abnormality of the bronchial tree is the crux of the problem in asthma. It seems to be closely related to the abnormality of the nose and the skin which we recognize clinically as rhinitis, urticaria and eczema. The schema shown in Figure 1 may be equally applicable in these conditions.

#### ACTH AND THE ADRENAL STEROIDS IN ASTHMA

Asthma arising on exposure to ragweed pollen in the course of the ragweed season tends to occur chiefly at night and not necessarily at those times when exposure is most intense.<sup>28</sup> Nevertheless, exposure in the laboratory to inhaled aerosolized extracts of pollen is followed by manifestations of asthma (reduction of the vital capacity, slowing of expiration, with or without overt symptoms) within a minute or so and these manifestations reach their peak within about six minutes. Complete or nearly complete recovery occurs within one-half to two hours or may be easily brought about by administration of a bronchodilator drug. Asthma is no less readily induced in this manner among those receiving ACTH or the adrenal steroids in doses known to be effective in relieving asthma occurring on spontaneous exposure to ragweed pollen as just described. This statement must be qualified by pointing out that the quantitative control of the dose of allergen administered by aerosol is so poor that some decrease in pulmonary responsiveness to the inhaled extract cannot be excluded. It does appear, however, that an allergen may act on the bronchial tree to produce an abrupt change which is not prevented by administration of adrenal steroids or to cause a slowly developing change which is reversible with these agents. The responsiveness to non-specific factors represented in Table I is likewise markedly diminished by steroid therapy as

judged by clinical experience. The relationship between the prompt and the more delayed symptoms following exposure to an allergen and the responsiveness to the "non-specific" factors mentioned earlier can be little more than a matter for speculation at this time.

TABLE I

Irritability of Bronchial Tree	Level of Allergy to One or More Substances			
0	0	+	++	+++
+	0	+	++	+++
++	0	+	++	+++
+++	0	+	++	+++

Neither ACTH nor cortisone appears to influence significantly the degree of skin reactivity to allergenic extracts or the titer of skin-sensitizing antibody,<sup>29-33</sup> although there is not complete agreement on this point.

#### THERAPEUTIC IMPLICATIONS

Many practical points are readily derived from our fresh and presumably incomplete knowledge of the functional changes which accompany asthma.

*Bronchial Asthma and Cardiac Failure.* As dyspnea is common to both asthma and cardiac failure, a therapeutic trial with bronchodilator drugs or the demonstration of bronchial obstruction (or the lack of it) by tests of pulmonary function is often helpful.<sup>10</sup> As dyspnea in both conditions may be paroxysmal and as signs of obstruction may be missing in the interval between attacks of asthma, a provocative test with histamine or mecholyl may be warranted.

The differential diagnosis of asthma and cardiac failure does not often present a problem; when the two coexist, it is helpful to define as clearly as possible what part each is playing because one condition tends to aggravate the other and successful treatment of existing asthma may greatly facilitate the management of cardiac failure. Both hypoxia and the increased work of breathing associated with bronchial obstruction tend to increase cardiac output and therefore relief of the obstruction with bronchodilator drugs or adrenocortical steroids (prednisone and prednisolone appear to be especially useful here) will usually more than balance the relatively trivial adverse effect which such drugs may have on cardiac failure. Striking aggrava-

tion of asthma may accompany cardiac failure and, with failure, asthma may appear for the first time. When this occurs the syndrome is usually called cardiac asthma, a rather poorly defined term which at times is extended to include acute pulmonary edema, apparently a quite different condition. "Cardiac asthma" is probably best applied to bronchial obstruction occurring only in the presence of cardiac failure, the congestion of the pulmonary bed perhaps acting as a "non-specific" but nevertheless intense stimulus to an already hyperirritable bronchial tree. The agents effective in the treatment of asthma will also temporarily relieve the obstructive manifestations of cardiac asthma and should be used in conjunction with therapy for the cardiac failure.

A middle course can usually be taken between the hypoxia which accompanies severe asthma, on the one hand, and aggravation of respiratory acidosis which may follow the administration of oxygen on the other. When oxygen is first given, careful observation of the patient is necessary for evidence of developing impairment of the sensorium. If this occurs, reversal of the effects should follow within a few minutes when administration of oxygen is stopped. By trial and error, a flow rate may be found (often about 2 L./minute) which can be safely given. As hypoxia increases cardiac output and may perhaps increase resistance to blood flow through the lung, oxygen is indicated in the presence of cardiac disease. Because of the artificial increase in respiratory dead space and possible aggravation of acidosis for this reason, a mask should not be used in giving oxygen to patients with asthma. Control of the oxygen concentration in a tent is exceedingly difficult and as it may also heighten anxiety and tend to remove the patient from ready contact with the nurse and physician, we believe that a tent is unsuitable in severe asthma. The nasal catheter, although possessing obvious disadvantages also, is nevertheless the safest and most practical.

Mechanical aids to respiration, although perhaps appropriate in the treatment of some instances of pulmonary emphysema, are not recommended for the treatment of asthma. The need for such measures will be rare indeed in a disease so readily treated with steroids.

Occasionally an understandable feeling exists among those taking care of asthmatic patients that the patient uses his disease to compel attention, that attacks are "put on." Such an inter-

pretation of asthmatic manifestations should, however, be viewed in the light of the following. First, there is ample evidence that the asthmatic attack is accompanied by extreme impairment in pulmonary function. Indeed what appear to be dangerous degrees of respiratory embarrassment, as determined by tests of pulmonary function, may be induced at will in the laboratory. Add to this the work involved in obstructed breathing and we have an entirely adequate explanation for the apprehension, dependance and the, at times, exasperating demands of the asthmatic patient. Calculated neglect of the patient's demands or heroic attempts to "break up the attack" with bronchoscopy or anesthesia are out of place. A second source of misunderstanding may be avoided if a clear distinction is made between the intensity of the asthmatic process on the one hand and the intensity of the clinical manifestations on the other. The need for this distinction arises because these two factors do not always vary together. For example, in the absence of any change in the intensity of the asthmatic process, the tendency to hyperventilation which accompanies anxiety may accentuate the auscultatory signs of asthma. If anxiety is allayed, less effort may be expended in respiration, the minute volume may diminish and the clinical manifestations may decrease without any change in the underlying process for the better. Here we have an "attack" produced by anxiety, "relieved" by reassurance. Conversely, sedation may decrease the effort to breathe with a consequent decrease in the manifestations and apparent relief of asthma. If this is accompanied by a decrease in minute volume and no improvement in pulmonary function, the stage is set for the development or aggravation of respiratory acidosis. It is undoubtedly for this reason that morphine is so dangerous in severe asthma. In addition to sedation, the administration of oxygen in the presence of a complicating respiratory acidosis will also decrease ventilation and diminish the physical signs of asthma. In these situations the danger is the illusion that the lung is performing better when in fact it is merely being driven less hard.

The unreliability of the intensity of auscultatory signs as an indication of the severity of asthma indicates that the obstruction in severe attacks may be of a type in which gaseous viscosity rather than turbulence predominates as the principal factor in resistance. This conclu-



sion finds support in the failure of a helium-oxygen mixture to improve significantly pulmonary function in patients with severe asthma.<sup>34</sup>

*Allergic Factors.* None of the more recent developments in our understanding and treatment have decreased the importance of either removal of allergenic factors in the environment or treatment with injections of suitably selected allergenic extracts. The correct selection of these is of immense importance and this step is unquestionably best undertaken by one who has had a good deal of experience. Indiscriminate administration of allergenic extracts leads not only to failure but also to an understandable reluctance among many critical physicians to subject their patients to this rather expensive and time-consuming procedure. There is a widespread belief among allergists, shared by the writer, that results with injection therapy in seasonal asthma is highly effective. The logical reason for this is that an allergic reaction is the cause of symptoms and identification of the causative agent in seasonal asthma is possible. On the other hand, identification of the cause in asthma occurring without any seasonal pattern is, at best, far less accurate and is frequently impossible. For this reason alone, injection therapy in such patients may be unsuccessful. Furthermore, if exposure to those allergens capable of aggravating asthma is only one of a number of factors in the production of symptoms, their removal may have little influence on the course of the illness.

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# Case Reports

## Potassium Depletion by Enemas\*

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OUTPUT of potassium from the gastrointestinal tract may exceed intake, and thus produce signs of hypokalemia, after vomiting, diseases of malabsorption, excessive use of laxatives or spontaneous diarrhea. The present study indicates that prolonged use of enemas also may increase gastrointestinal potassium excretion sufficiently to induce severe hypokalemia.

### CASE REPORT

Patient R. R., a twenty-nine year old white man with extensive paralytic residua from a previous attack of poliomyelitis, was admitted to the Northwest Respirator Center on October 18, 1953, acutely ill with severe respiratory distress, marked weakness, high fever and chills. His illness began in August, 1951, when acute bulbospinal poliomyelitis developed which required continuous treatment by tank respirator. This illness was complicated by sensory loss below the L-4 dermatome with saddle anesthesia and loss of control of the bladder and anal sphincters.<sup>12</sup> A large sacral decubitus ulcer developed. Moderate improvement of upper extremity and respiratory function occurred during convalescence so that eventually the patient was able to breathe without a respirator, except during the night. No sensory or motor function returned in the lower extremities, however. Urinary incontinence and great difficulty with fecal evacuation persisted but the patient eventually returned home in November, 1952. There he received prolonged enemas with protracted abdominal and rectal manipulations to produce fecal expulsion. Enemas often were preceded by cathartics. An acid-ash diet was prescribed in December, 1952, because of a renal stone and infection of the urinary tract. This diet contained almost no fruit juices or potatoes, and from food tables its potassium content was calculated to be about 40 mEq. Infection of the urinary tract recurred, however, finally precipitating the present hospital admission.

On admission the patient was frightened, extremely weak and required a tank respirator continuously. Temperature was 39.4°C. Skin and mucous mem-

branes were dry. Bilateral flank tenderness was present. Physical examination was otherwise normal except for asymmetric, atrophic residual paralysis in his upper extremities, neck, trunk and respiratory muscles. The patient was hypesthetic below the L-3 dermatome, anesthetic below the L-5 dermatome and had advanced symmetric atrophic paralysis of the lower extremities. Urine output in the first twenty-four hours was 150 cc. Laboratory data are tabulated in Table 1.

In spite of the low urine output large potassium supplements were given slowly, as noted in Table 1, so that by the fourth day serum potassium was restored to normal. Repletion was accomplished with careful supervision by serial electrocardiograms. Although the patient was stronger and required less ventilation by this time, he still required the respirator continuously. He was able to breathe without assistance for one hour on the fifth day and gradually increased his strength and independent breathing after that time. Figure 1 diagrams the early clinical course.

At the end of the first week serum electrolyte levels had been restored to normal. They remained within normal limits throughout the remainder of the study. During convalescence, intravenous pyelography demonstrated a left renal calculus. The blood urea nitrogen, creatinine clearance and ability to concentrate and dilute urine were within normal limits. Two months after admission the patient had the renal stone removed and the decubitus ulcer healed successfully. Following these procedures the enema studies herein reported were carried out and a general rehabilitation program was instituted. The patient responded well to bowel training and management so that eventually only two enemas per week were required, with less expenditure of time and effort. In May, 1954, the patient was discharged from the hospital on a diet of 0.5 gm. of calcium and daily supplements of 3.0 gm. of potassium chloride. Since then no further difficulties have occurred and the patient requires the respirator only for sleeping.

### SPECIAL STUDIES

In the hospital tap water enemas were given to patient R. R., without previous cathartics.

\* From the Division of Neurology, Department of Medicine, University of Washington School of Medicine. Aided by an annual grant from The National Foundation for Infantile Paralysis, Inc. to the Northwest Respirator Center.

TABLE I

Date	Blood Urea N. (mg. %)	Serum				Total Serum Protein (gm. %)	K Intake (mEq.)	Urine K (mEq.)	Electrocardiogram
		CO <sub>2</sub> (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)				
10/19	6.2	16	96	139	1.1	4.8 (albumin 2.4)	227	14.2	Prolonged Q-T, low T <sub>1</sub> , aVL, aVF
10/20	....	13	101	145	2.1	.....	225	13.0	Prolonged Q-T, flat T <sub>1,3</sub> , aVL
10/21	10.2	24	100	147	3.7	.....	80 + D*	5.4	Less prolonged Q-T, Ca 8.9 mg. %
10/22	5.9	32	97	141	4.0	.....	80 + D	....	Normal
10/23	9.9	29	103	144	3.9	.....	80 + D	....	.....
10/30	....	26	99	145	4.6	.....	D	....	.....
11/2	....	25	105	148	4.4	7.5 (albumin 3.8)	D	....	.....

\* D = diet (calculated to provide 65 to 90 mEq. potassium per day).

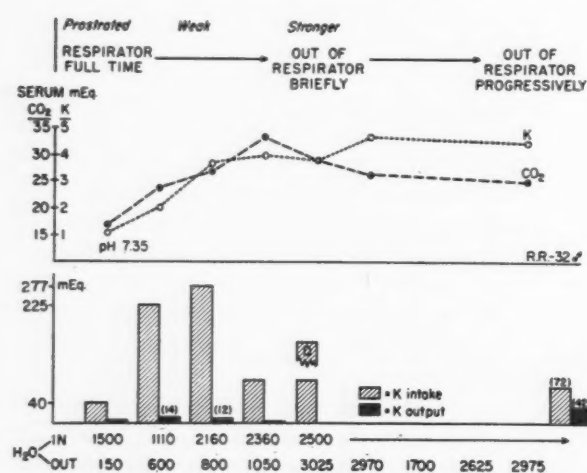


FIG. 1. Patient R. R. Potassium deficiency secondary to enemas. Course during first nine days in the hospital: pH—arterial blood pH; D—diet. Remainder of intake is tube feeding and infusion; output—urine only (no stool or enema during first five days).

During early convalescence these were administered to simulate those given at home, the volume ranging from 1,500 to 3,500 cc. Returns varied from 750 to 4,600 cc. Enema returns were measured, homogenized and wet ashed, and an aliquot was analyzed for potassium with a Baird flame photometer. Blood was drawn pre- and post-enema, and serum potassium was analyzed by flame photometer. Diets were calculated from standard tables.

The enema returns varied in potassium concentration from 12 to 87 mEq./L. (Table II.)

TABLE II

Date	Fluid In (cc.)	Fluid Out (cc.)	Enema K (mEq.)	Urine K (mEq.)	Diet K (mEq.)
12/28	.....	4,600	258.5	....	G. W. *
12/31	.....	1,100	95.9	....	G. W.
1/4	.....	1,000	78.8	....	G. W.
2/25	1,700	950	32.7	....	G. W.
2/27	1,400	2,000	68.4	....	G. W.
3/2	2,800	2,400	13.4	37.6	G. W.
3/11	.....	.....	.....	65.1	G. W.
3/12	2,400	1,200	12.0	21.8	G. W.
3/13	.....	.....	.....	37.5	G. W.
3/15	.....	.....	.....	43.1	G. W.
3/16	2,400	2,400	106.0	55.6	G. W.
3/17	.....	.....	.....	66.3	G. W.
4/11	.....	.....	.....	....	54
4/12	2,700	2,100	11.1	42	72
4/13	.....	.....	.....	35	87
4/14	.....	.....	.....	75	111
4/15	1,700	1,400	43.4	66	94
4/16	.....	.....	.....	....	85

\* G. W. = general ward diet, 75 ± 10 mEq.

The total potassium obtained from individual enemas varied from 12 to 256 mEq. There was little correlation between the amount of fecal fluid and the total potassium loss. It was our impression, however, that prolonged retention of enema fluid resulted in greater potassium wash-out in the efflux.

From these data it is estimated that patient R. R. may have lost as much as 500 to 1,000



mEq. of potassium per week in his stool if enemas given at home were similar to those given experimentally. During hospitalization these losses of potassium were reduced to 100 mEq. per week by improving the management of his bowel care and reducing the number and volume of enemas.

At the time of the experimental observations on enema contents, performed when his acute potassium depletion had been corrected, patient R. R. failed to conserve urinary potassium on the day of or the day following an enema. (Table II.) He could conserve potassium when sufficiently depleted, however, since loss of urinary potassium was as low as 5.0 mEq. per day shortly after admission. (Table I.)

#### COMMENTS

Profound weakness and a serum potassium level of 1.1 mEq./L. were signs of severe potassium depletion in patient R. R. The acidosis that was present (serum bicarbonate = 16 mEq./L., arterial pH 7.35) made the low serum potassium level even more significant since acidosis experimentally causes transfer of potassium out of the cells, with elevation of the serum level.<sup>16</sup> Why he was so depleted of potassium was at first unclear. He had been on an acid-ash diet which provided a daily potassium intake of about 40 mEq. This would not have put him into negative balance without excessive potassium losses.

Ample data demonstrate that the human kidney conserves potassium rapidly when intake is limited, although this conservation is less in rate and degree than renal sodium conservation. Thus Milne and Black<sup>10</sup> found that urinary potassium was reduced to 20 mEq. per day by the fifth day on a diet containing 14 mEq. potassium. Blahd and Bassett<sup>1</sup> noted a similar conservation on a diet containing 15 mEq. potassium although the urinary potassium output leveled off at 20 mEq. per day and continued at that level for the remainder of the fifty-five days of their study. Weston et al.,<sup>22</sup> however, were able to decrease urinary potassium excretion to as low as 1 mEq. per day during oral resin therapy. Other workers<sup>6</sup> have found that this renal conservation mechanism withstands hyperventilation, osmotic diuresis or bicarbonate ingestion—stimuli which normally cause large urinary potassium excretion. There was little to suggest that potassium depletion in this patient had resulted from excess urinary

loss of this ion, since function of the kidney was normal during later studies. Similarly, his estimated skin loss of a maximum of 4 mEq. potassium per day<sup>1</sup> hardly seemed sufficient to account for the depletion. Hence an extra-renal loss was sought.

The history of prolonged daily enemas often requiring large volumes of fluid and producing several liters of washout seemed a potential source of potassium loss; the subsequent experimental demonstration of 12 to 256 mEq. of potassium content per enema confirmed this hypothesis. This much daily potassium washout could readily produce depletion sufficient to cause hypokalemia in a man ingesting only 40 mEq. of potassium each day. Reduced potassium reserves, resulting from extensive paralytic muscle wasting,<sup>2</sup> may have accelerated the rate at which depletion appeared. Other paralyzed patients being studied at the present time in this laboratory have had significant potassium excretion in enema washouts.

It has not been possible to find in the literature other studies in which the amount of potassium washed out by enemas was measured. However, there are data available indicating that the colon is a potential route of large potassium losses.<sup>4,5,21</sup> Schwartz and Relman<sup>15</sup> observed potassium depletion following watery diarrhea (containing 55 mEq./L. of potassium) in two otherwise healthy women habituated to laxatives. Omission of the laxatives and institution of an ordinary ward diet were sufficient to return the serum potassium to normal limits in these women. The diarrhea produced by para-amino salicylic acid causes potassium depletion in the same manner.<sup>15</sup> Studies of electrolyte transfer in an isolated loop of human transverse colon<sup>17</sup> indicate that potassium may be lost into the lumen against a gradient as high as 80 mEq./L. Potassium depletion, together with acidosis, develops in patients after uretero-colonic transplants.<sup>11</sup> This is at least in part the result of potassium loss by secretion or membrane transfer into a bowel distended by large urine volumes.<sup>3,14</sup>

Profound weakness may develop insidiously in patients with Hirschsprung's disease, sometimes with death.<sup>9</sup> In one patient reported by Richards and Hiatt<sup>13</sup> a low serum sodium was observed following an enema. The serum sodium was elevated to normal levels by proctoclysis of 5 per cent NaCl. Coincident with the rise in serum sodium there was a fall in serum potassium

from 4.4 to 2.5 mEq./L.; the cause of this potassium loss was not further explored. Loss of potassium via enema has not been specifically described in Hirschsprung's disease but it appears possible that the repeated enemas given to patients with this illness could cause chronic potassium depletion and hypokalemia.

Routine preparations for bowel surgery, gastrointestinal x-rays and intravenous pyelograms often require laxatives and "enemas until clear returns." Such repeated enemas together with a preoperative diet low in potassium, due to missed meals and intravenous fluids, might contribute to postoperative hypokalemic alkalosis.

In the patient observed in this study serious potassium losses developed as the result of repeated enemas and cathartics. This emphasizes the need for particular training in bowel care for patients with lesions of the spinal cord, lumbosacral nerve roots or bowel autonomic plexi, who so easily develop dilated atonic colons. If repeated enemas are necessary for these patients, sufficient potassium intake should be provided to compensate for electrolyte losses in excess of normal metabolic needs.

#### SUMMARY

Repeated prolonged enemas, often preceded by administration of cathartics, resulted in profound hypokalemia and weakness in an adult male suffering extensive muscle paralysis and a cauda equina nerve root lesion. Dietary potassium had been restricted to approximately 40 mEq. daily during the period that deficiency developed. Returns from experimental enemas given to this patient had potassium contents as high as 256 mEq. Potassium loss seemed to be greater when contact between infused enema fluid and the dilated atonic bowel was prolonged. Similar depletion might be expected in patients with Hirschsprung's disease and neurogenic atony of the bowel who require repeated enemas.

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# Scleroderma of the Kidneys\*

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THE purpose of this paper is to discuss from a clinicopathologic standpoint the renal changes involved in scleroderma. The protean manifestations of scleroderma or progressive systemic sclerosis are widely recognized. A large series of cases describing gastrointestinal, cardiac or pulmonary changes characteristic of the disease have been reported.<sup>1,4,5,14</sup> Study of autopsy protocol of previously reported cases reveals, as an infrequent finding, changes in the renal arterioles and arteries which may be considered pathognomonic of scleroderma.

The following is a fatal case of scleroderma in which the changes were limited to the skin and kidney. The terminal hospitalization was characterized initially by convulsive seizures accompanied by severe hypertension with proteinuria, cylindruria and hematuria. The convulsions, probably due to cerebral edema, were controlled by lowering the blood pressure. An acute form of uremia with oliguria accounted for the patient's death. Besides the characteristic changes in the skin postmortem examination showed a patchy cortical necrosis of the kidneys, fibrous thickening of the intima of the interlobular arteries, and fibrinoid necrosis of the arterioles and the distal portions of the interlobular arteries in the involved areas.

## CASE REPORT

This twenty-six year old white housewife, mother of one child, had been discharged from the Clinical Center of the National Institutes of Health at Bethesda, Maryland, in December, 1953, with the diagnosis, confirmed by biopsy, of generalized scleroderma. Two years previously she had noted blueness of her legs on exposure to cold, and one and a half years previously swelling of her hands and feet, along with tenderness of the skin and generalized aches and pains aggravated by motion. The clinical diagnosis of scleroderma was made for the first time in October, 1952, but a biopsy of her skin, at that time, gave negative results.

Scleroderma progressed rapidly despite treatment which included adrenal cortex extract, thyroid extract, tolserol,<sup>®</sup> paraffin baths, priscoline,<sup>®</sup> vitamin E, cortisone, artane,<sup>®</sup> frequent injections of penicillin in conjunction with oral pyribenzamine,<sup>®</sup> and extensive physiotherapy. A complete diagnostic study during her four months of hospitalization revealed that the scleroderma was limited primarily to the skin, with flexion deformities of the joints of the fingers and elbows associated with limitation of abduction of shoulders, plantar flexion of ankles and flexion of hips and knees. Barium swallow revealed no indication of involvement of the esophagus. X-rays of the hands and feet showed resorption of the terminal phalanges bilaterally. The blood pressure ranged between 96/60 and 115/80. The urine was normal, as was the creatinine clearance.

Following discharge from the hospital physiotherapy was continued at the Maxwell Air Force Base Hospital. The patient's complaints were limited to stiff and tender skin and painful contracted joints until, three days prior to her admission on July 6, 1954, blurring of vision was noted. On the morning of admission the patient's husband observed that her eyelids were puffy. On the afternoon of the day of admission the patient was found unconscious on the floor of her home and was brought to the emergency room of the hospital where a grand mal seizure was witnessed. Sodium amytal<sup>®</sup> (7½ gr.) was administered intravenously, with control of the convulsion.

The patient was in a semi-comatose state when admitted to the hospital. Rectal temperature was 98°F.; pulse 120; blood pressure, 170/130. Examination of the eyes revealed constricted and equal pupils and in both fundi small patches of white exudate with marked narrowing and tortuosity of the small arterioles. The retinal veins were full. The disc margins were indistinct but there did not appear to be definite papilledema. The heart was not enlarged; there was a sinus tachycardia of 120 with a grade 2 apical systolic murmur; P<sub>2</sub> was greater than A<sub>2</sub>. No stiffness of the neck was present. The deep tendon reflexes were equal bilaterally. Babinski or Hoffmann signs were not noted. The skin over the fingers was smooth, white and shiny, while the skin over the

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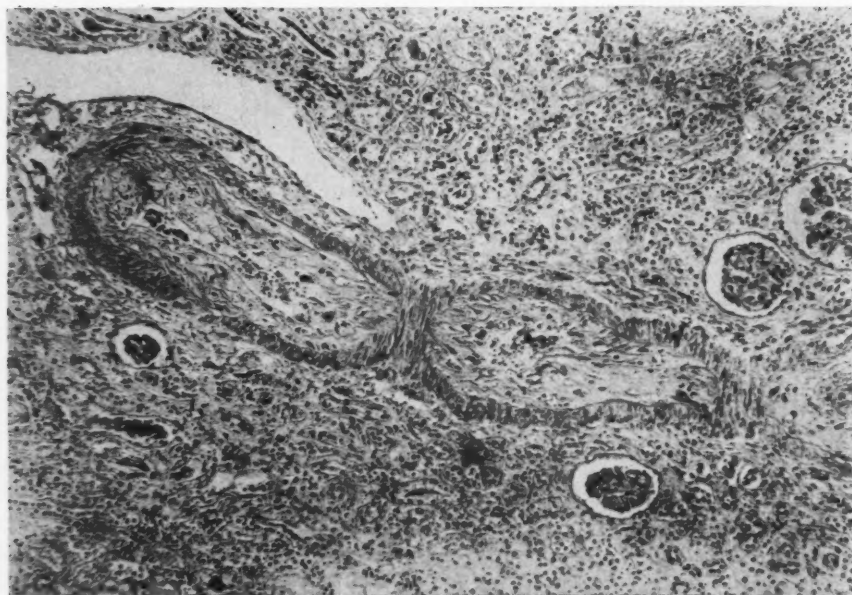


FIG. 1. Interlobular artery showing subintimal proliferation; original magnification,  $\times 110$ .

hands, forearms, face, chest and legs was dark, thick and inelastic. Edema of the forehead was present which pitted only on firm and prolonged pressure. There were flexion contractures of the knees, fingers, elbows and hips. The mouth could not be opened more than 2 cm.

Urinalysis on admission revealed a 4+ albumin with three to five white blood cells, seven to nine red blood cells, and one or two granular casts per high power field. The specific gravity was 1.010. White blood count was 24,500, with 89 per cent neutrophils, 7 per cent lymphocytes and 4 per cent band forms. The hematocrit was 43 per cent. A preparation for lupus erythematosus cells was negative. The blood urea nitrogen was 33 mg. per cent; the total protein 6.6 gm. per cent, with 3.2 gm. per cent albumin and 3.4 gm. per cent globulin.  $\text{CO}_2$  combining power was 39 volumes per cent; calcium, 11.3 mg. per cent; phosphorus, 3.9 mg. per cent; chlorides, 556 mg. per cent.

X-ray of the chest was technically poor but no abnormalities were noted. The electrocardiogram showed a sinus tachycardia of 144 with depressed RS-T segments in 1, 2, 3, AVF,  $V_4$ ,  $V_5$  and  $V_6$ . T waves were low in 1, and diphasic (— +) in 2, 3, AVF,  $V_4$ ,  $V_5$  and  $V_6$ . The electrocardiogram was interpreted as being abnormal and it was thought that some of the changes might be due to the rapid rate or ventricular strain. A lumbar puncture revealed normal pressure with clear acellular fluid; the total protein was 56 mg. per cent.

The patient continued in a semi-comatose state during the remainder of the first day. Despite intramuscular paraldehyde and 50 per cent magnesium sulfate the blood pressure continued to rise and the patient experienced further generalized convulsions.

Eight hours after admission she was deeply comatose with Cheyne-Stokes respiration and was considered to be moribund; blood pressure was 250/150. At that time 10 mg. of apresoline hydrochloride were given intravenously, with resultant lowering of blood pressure to 200/140 and cessation of convulsions.

On the second hospital day the blood pressure was maintained in a range of 170 systolic by 10 mg. injections of apresoline hydrochloride intramuscularly. By the third hospital day the patient was fairly alert and was able to take fluids and food by mouth. The urine on the fourth day showed 4+ albumin. In each high power field there were four to five red cell casts and red blood cells too numerous to count.

Clinical improvement continued until the sixth day when the patient had another convulsion accompanied by a blood pressure of 240/150. As a therapeutic procedure in addition to intramuscular apresoline hydrochloride, 300 cc. of blood were removed. Later the same day it was noted that the stools were dark and gave a 4+ guaiac reaction for blood. The hematocrit at that time was 29 per cent. Because of the possibility that apresoline and not uremia might have been implicated in this gastrointestinal bleeding, administration of veriloid® in amounts as high as 1 mg. every six to eight hours intramuscularly was started. The blood pressure was thereafter maintained at or below 200 systolic.

On the seventh hospital day the patient was less alert; the blood urea nitrogen was 69 mg. per cent;  $\text{CO}_2$  combining power, 34 volumes per cent; chlorides, 490 mg. per cent; hemoglobin, 9 gm. per cent; hematocrit, 27 per cent. At this time it was noted that the disc margins were still indistinct; there were no retinal hemorrhages. On the eighth hospital day the hematocrit was 16 per cent and the hemoglobin, 6.3

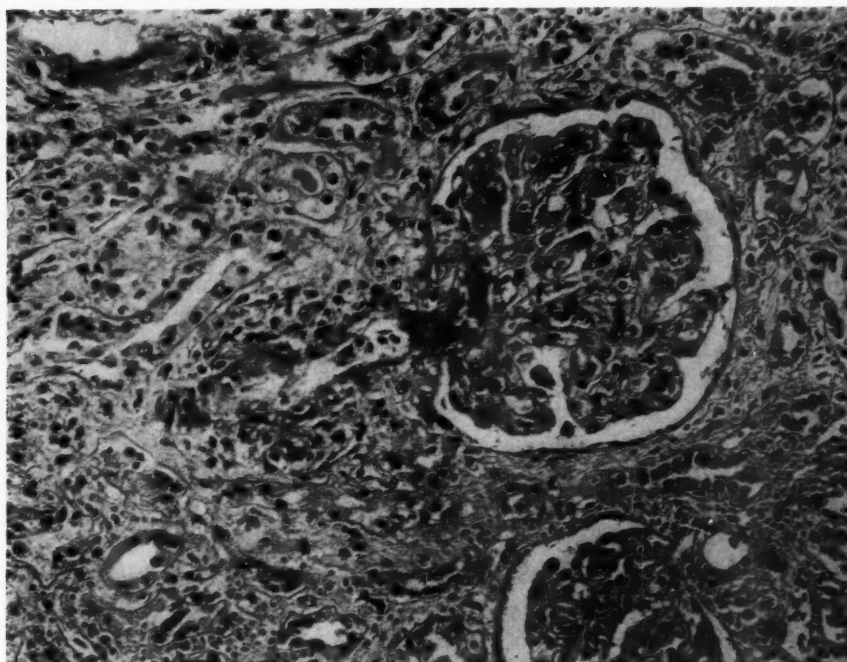


FIG. 2. Arteriole and glomerulus showing fibrinoid necrosis; original magnification,  $\times 225$ .

gm. per cent. Thirteen hundred cc. of blood were given slowly without event.

A transient improvement in the patient's condition was noted. However, the blood urea nitrogen steadily rose and the urine output diminished. On the ninth hospital day the blood urea nitrogen was 102 mg. per cent and the urine output 60 cc. On the eleventh hospital day the patient was started on gantrisin® therapy for pyuria due to *Pseudomonas aeruginosa* which had probably been introduced by the indwelling catheter. From then on her condition deteriorated steadily. By the thirteenth day the systolic blood pressure remained below 200 without the use of veriloid. Blood urea nitrogen on the fourteenth hospital day was 141 mg. per cent with a  $\text{CO}_2$  combining power of 23 volumes per cent. In addition to the measures and medications mentioned the patient was given parenteral fluids, penicillin, digitalis and mercurhydrin. She died quietly on the seventeenth hospital day. During the preceding eight-day period she had excreted a total of only 375 cc. of urine.

The clinical diagnosis was generalized scleroderma involving the skin and kidney, with death due to uremia.

At autopsy it was noted that the skin over the extremities, neck, face and shoulders was dry, inelastic and showed increased pigmentation. The toughness and inelasticity of the skin was less obvious over the trunk. Pitting edema was present over the ankles.

Approximately 500 cc. of clear yellow fluid were present in the abdominal cavity. There were only a few cubic centimeters of fluid within the pleural

cavities. The heart was not enlarged. The great vessels had their normal positions and distributions. The lungs were edematous. The spleen and liver were not enlarged. The gastrointestinal tract was patent throughout with no areas of thickening or ulceration. Together the kidneys weighed 400 gm. and were of approximately equal size. Both organs were pale and swollen and on cut section the cortices presented a mottled reddish white coloration. The gross picture of the kidneys was that of a patchy cortical necrosis. The brain was not remarkable except for edema.

Microscopic sections of skin showed the typical epithelial atrophy and dermal fibrosis of scleroderma. Sections of kidney showed a patchy cortical necrosis with blood vessel involvement. The vascular involvement was of two types. The interlobular arteries showed fibrous thickening of the intima, greatly reducing the size of the lumens. The distal portions of the interlobular arteries and the arterioles in the involved areas showed a definite fibrinoid necrosis, some with thrombi in the lumens. This necrosis extended into the glomeruli. (Figs. 1 and 2.)

Occasional blood vessels showing hyaline thickening of the walls were present in the pancreas and spleen. Vascular involvement in the other organs of the body was not demonstrated.

#### COMMENTS

Review of the literature on scleroderma reveals that specific involvement of the kidney in this disease has rarely been reported. According to Allen<sup>2</sup> the peculiar edema and lamination



of the intima of the renal interlobular arteries is an infrequent finding in scleroderma that resembles a change of malignant nephrosclerosis. He states further that "wireloop" glomerular changes have been observed in scleroderma but on rare occasion.

Recently, Moore and Sheehan<sup>10</sup> made a study of renal lesions in three patients who died with scleroderma. The microscopic picture was essentially the same in all three cases and resembled the findings in our case. There was patchy necrosis of the cortices. Two distinct types of arterial lesion were described. In the first nearly all the interlobular arteries showed at about the point of origin a gross and quite concentric intimal thickening which had a rather mucoid appearance with relatively few nuclei. In the second, the peripheral parts of many of the interlobular arteries and some of the afferent arterioles showed a fibrinoid necrosis of the media and intima. Often the affected artery contained a thrombus either forming a thick layer over the intima or occluding the lumen completely. Clinically, two patients died in acute uremia; in one patient in whom the urine output was recorded there was terminal oliguria. Clinical data were incomplete in the third case. In no patient was marked hypertension noted.

Similar pathologic changes have been found in the kidneys of sclerodermatous patients treated with cortisone and corticotropin. In part these changes had been attributed to those drugs. The cases which were in common with ours presented hypertension as a prominent clinical feature. In one<sup>12</sup> of these cases there was progressive development of hypertension during two months of cortisone therapy. Despite cessation of treatment continued elevation of the blood pressure occurred with convulsions and eventual death in acute uremia. In this patient marked intimal thickening of renal interlobular arteries with almost complete obliteration of the lumens was present. In a second case<sup>7</sup> which was of a fulminant nature no improvement was noted following four days of corticotropin treatment. In addition to clinical findings of jaundice and cardiac failure, uremia and oliguria were present, with death following a convulsion. Autopsy revealed an acute fibrinoid necrotizing process affecting the serosal and synovial membranes, the arterioles and small arteries generally, and the glomeruli. The third patient<sup>5</sup> was first noted to have hypertension two to

three months following a course of corticotropin therapy. Within a few days cerebral hemorrhage developed from which the patient was recovering until a fatal recurrence two weeks later. During her terminal illness there was albuminuria and microscopic hematuria, and the serum non-protein nitrogen was elevated to 50.5 mg. per cent. Severe renal arterial and arteriolar intimal proliferation, with occasional disruption of the entire vessel wall, was evident on pathologic examination.

Prior to the use of cortisone and corticotropin in the treatment of scleroderma, hypertension and renal insufficiency had been observed as a part of the clinical picture. The characteristic lesions of intimal proliferation and fibrinoid necrosis were reported in those patients<sup>3,4,11,13</sup> and had been noted in other patients<sup>6,8,14</sup> without definite clinical evidence of renal involvement. In one case<sup>14</sup> there was only intimal proliferation. In two reported cases,<sup>3,9</sup> thickening of the basement membranes about the glomerular capillaries was described.

We believe that the renal changes noted in our patient and in those cited are a manifestation of the basic pathologic process of scleroderma. Since neither hypertension nor clinical evidences of renal disease was noted until eighteen months following cessation of cortisone therapy, it is improbable that cortisone played a part in our patient's terminal illness.

#### SUMMARY

A case of scleroderma limited to the skin and kidneys is presented. Review of the literature and experience with this case indicate that the development of hypertension or clinical evidence of renal involvement is a grave prognostic sign.

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# Congenital Hemorrhagic Diathesis of the Prothrombin Complex\*

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THE study of congenital hemorrhagic diatheses has clarified the role of specific factors in blood coagulation and the patterns of bleeding found. It is of considerable interest, therefore, to be confronted with a patient exhibiting a congenital deficiency of prothrombin, factor VII, and thromboplastin generation similar to that induced by dicumarol. Her remarkable history of bleeding since early childhood documents the clinical manifestations of this defect. Plasma was shown to have a prolonged beneficial effect unrelated to the amounts of known clotting factors supplied. This observation invites new considerations of the mechanisms involved in synthesis or destruction of prothrombin and factor VII.

## CASE REPORT

R. G., born in 1922, recalled bleeding first at the age of three or four years when she suffered from recurrent bloody diarrhea. Hematuria began when she was five years of age and continued intermittently thereafter. In the pre-school period joint pains were of sufficient severity to confine the patient to bed for several days at a time. The arthritic pains were never accompanied with obvious joint effusion. When eight years old she experienced sudden swelling and discoloration of both legs. This condition persisted through the summer. It began in the lower portion of the legs and may have followed trauma. Pain was severe, and after some time both legs were incised and drained.

During the subsequent four years there were repeated episodes of joint pain and hematuria. Menstruation began when the patient was twelve years old and was thereafter excessive in amount. Dilatation and curettage was performed the following year, with little or no effect on the menorrhagia. During the next twenty years this operative procedure was repeated four times without effect. The excessive blood loss had

produced anemia on many occasions, with prompt response to iron therapy. During adolescence there were frequent ecchymoses and occasional petechiae in addition to the previously mentioned types of bleeding. When the patient was seventeen years of age, partial tonsillectomy was performed but the operation was discontinued because of profuse hemorrhage. Four transfusions were given at this time before bleeding stopped.

While attending college the patient experienced severe headaches, nausea and vomiting, ataxia and visual disturbances including homonymous hemianopsia. Weakness of the left arm and leg was demonstrated and optic disks were said to be choked. These symptoms and signs disappeared spontaneously. At the age of twenty the patient had an attack diagnosed as bronchopneumonia, associated with profuse bloody sputum. Joint pains and hematuria at times were very severe. On one of these occasions the hematuria was demonstrated by cystoscopy and ureteral catheterization to come from the kidney. Over a period of six months' hospitalization in 1942 she received between ten and twenty transfusions. During the following two years there were several episodes of pulmonary infiltration with extensive hemoptysis again necessitating frequent transfusions. Another attempt to remove tonsillar tissue was followed by severe hemorrhage and transfusions.

The following six years, between 1944 and 1950, were characterized by increasingly severe symptoms. In addition to joint pains, hematuria, hemoptysis and large subcutaneous ecchymoses, she began to have attacks of severe abdominal pain associated with fever. The more debilitating episodes were associated with generalized lymphadenopathy and splenomegaly. In 1949, following such an illness associated with a loss of weight from 156 to 112 pounds, she was considered to have "splenic anemia." The recommended operative intervention was refused by the patient.

Her family history was of interest in that an uncle was said to have died from bleeding after a biopsy of a

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TABLE I  
RECALCIFICATION TIME (MIN.)

Temperature	Control	C:9, P:1	C:7, P:3	C:5, P:5	C:3, P:7	C:1, P:9	Patient
25°C.	3.2	3.2	5.1	....	8.3	13	15
	3.3	5.4	20	20	20	20	20
37°C.	1.3	1.7	....	3.4	....	10	10

skin lesion. An aunt had a child who died at the age of six months with a "hematoma on the skull." Both parents are normal and show none of the laboratory abnormalities found in this patient. While the patient has worked as a nurse and x-ray technician for the past fourteen years, there are no blood changes to suggest harmful exposure to irradiation. The x-ray machine during this time has been properly monitored and only diagnostic procedures have been performed by the patient. The possibility of self-administration of dicumarol or drugs with similar effects has been completely excluded.

Although it cannot be definitely stated that this patient's disease is congenital, it is established that it has been present since early childhood and has continued throughout her life. The bleeding has characteristically produced large ecchymoses rather than petechiae. The locations of bleeding with their attendant symptoms have led to a great variety of diagnoses, as follows:

Diagnosis	Related Symptoms
Colitis	Bloody diarrhea
Acute nephritis	Hematuria
Rheumatic fever	Joint pains
Endometrial hyperplasia	Menorrhagia
Brain tumor	(Headache), visual disturbances, choked discs, ataxia
Bronchopneumonia	Pulmonary infiltration
Surgical condition of abdomen	Abdominal pain, palpable masses
Splenic anemia	Iron deficiency anemia and palpable spleen
Collagen disease	Diffuse symptoms, palpable spleen, fever and adenopathy

In retrospect, it seems amazing that the diagnosis of primary hemorrhagic diathesis was not made until 1949. Results obtained at this time revealed a prothrombin complex deficiency. Some response to vitamin K derivatives was noted but practical management has required that the patient receive fresh plasma transfusions at three- to five-week intervals. This has been done since 1949 and she has not had a major bleeding episode since that time. Pregnancies in 1953 and 1954 have terminated in spontaneous abortion at three and

a half months in each instance, with premonitory bleeding but no excessive hemorrhage at the time of abortion. In 1954 a second attempt was made to determine more precisely the nature of the clotting problem. The studies during both of these periods are presented.

## METHODS

Initial studies were performed in 1949. The bleeding time (Duke), clotting time (Lee-White), prothrombin consumption, recalcification time, cross mixing of plasmas in the study of anticoagulant activity, fibrinolysis, tourniquet test, platelet count and semi-quantitative clot retraction were measured by standard methods.<sup>1</sup> Other tests included the Quick prothrombin method,<sup>2</sup> antithrombin determination,<sup>3</sup> protamine titration<sup>4</sup> and fibrinogen analysis.<sup>5</sup> Recent studies (1954) include, in addition to the procedures mentioned, the one-stage methods for prothrombin,<sup>6</sup> factor VII (proconvertin, SPCA),<sup>6</sup> and factor V (labile accelerin, Ac-globulin),<sup>\*</sup> thromboplastin generation test<sup>8</sup> and clot retraction.<sup>9</sup>

## RESULTS

Since repeated determinations of various coagulation tests have been made, specific data are presented only when results have been abnormal. Bleeding time has been variably prolonged but only markedly during the patient's most severe hemorrhagic episodes. Platelet count has varied within normal limits. Clotting time was usually normal but has been prolonged to as much as sixty-five minutes during hemorrhage. Recalcification time has also been prolonged in a similar manner. Recalcification time of mixtures of the patient's and normal plasma indicated an anticoagulant action of the patient's plasma (Table I), although the effect was variable and not pronounced. Clot retraction has always been 50 per cent or more after incubation at 37°C. for four hours. Fibrinolysis have never been demonstrated. The tourniquet test was always negative. Prothrombin time (Quick) has been markedly depressed. Prothrombin consumption

\* The method for factor V determination is principally the same one-stage technic as described in reference 6. A plasma obtained by bubbling air through oxalated plasma for three days at room temperature serves as a factor V-free reagent.<sup>7</sup>



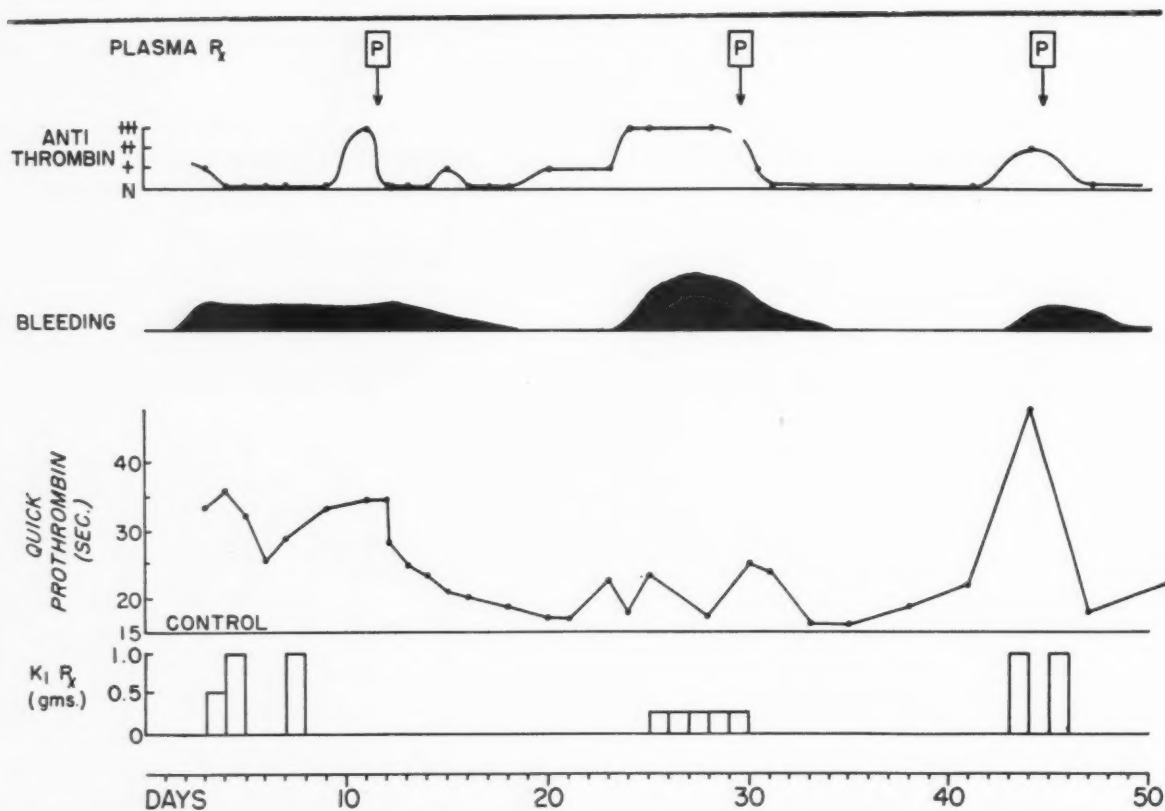


FIG. 1. The correlation of bleeding episodes, prothrombin time (Quick) and antithrombin titer are shown. The maximum (4+) antithrombin elevation corresponds to the result in Table III.

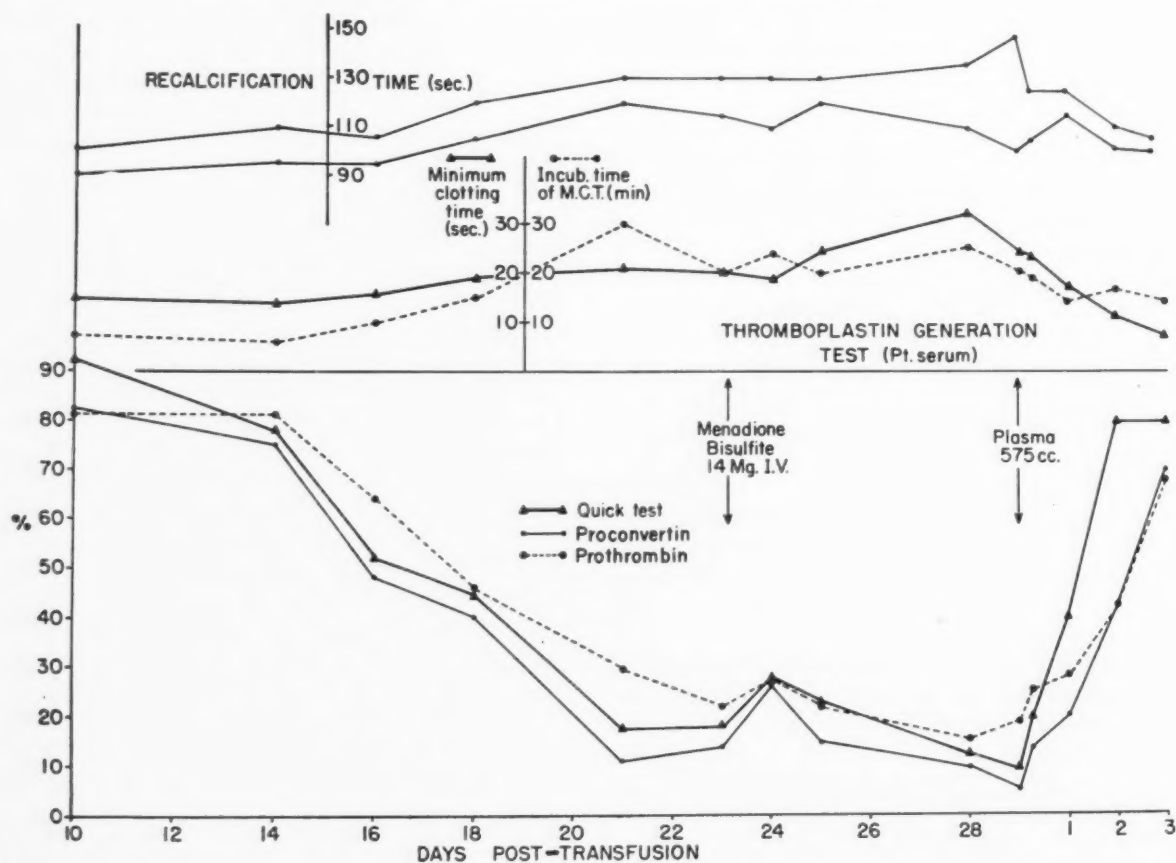


FIG. 2. Course, 1952. Recalcification time shows time from first fibrin to solid clot. Thromboplastin generation test shows the shortest clotting time achieved in the mixture (M.C.T.) and the time elapsed from the start of incubation until the minimum clotting time is reached (e.g., in Figure 3, C., M.C.T. = 14 seconds and incubation time = 1 minute). These reflect activity and slope of the thromboplastin generation curve.

TABLE II  
ELECTROPHORETIC ANALYSIS OF PLASMA (GM./100 ML.)

Subject	Total Protein	Albumin	Total Globulin	$\alpha_1$	$\alpha_2$	$\beta$	F*	$\gamma$
Normal.....	7.3	3.9	3.4	0.58	0.76	1.01	0.28	1.05
Patient (remission).....	5.8	3.4	2.1	0.39	0.41	0.68	0.32	0.59
Patient (relapse).....	5.9	3.4	2.1	0.39	0.41	0.68	0.39	0.59

\* Fibrinogen.

was normal when prothrombin activity had been increased through treatment. While interpretation was more difficult at lower levels of prothrombin activity, the prothrombin present was largely consumed. Tests for antihemophilic globulin activity employing one part of patient's blood and nine parts of

episodes and both the prothrombin time (Quick) and the slightly elevated antithrombin titer during the period from 1949 to 1950. (Fig. 1.) At this time her disease was severe. Results obtained during the second period of study in 1954 confirmed those obtained in 1951 except that the clotting and recalcification times

TABLE III  
ANTITHROMBIN, MAY 15, 1951

Tube	Thrombin (units)	Clotting Time (sec.)	
		Patient	Control
1	6	90	30
2	8	40.2	18
3	10	10.8	10.8

hemophilic blood resulted in the reduction of clotting time of hemophilic blood to the clotting time of the patient's. The Tiselius pattern\* of this patient's plasma during relapse and remission showed no significant change. (Table II.) Increase in antithrombin content of the patient's plasma was demonstrable using dilute thrombin solution. The prolonged clotting time of patient's plasma after addition of thrombin as compared to the control is illustrated in Table III. It should be noted that this difference from the control is not sufficient to account for the changes in the Quick prothrombin time, nor is it adequate to have caused bleeding in itself. Since lymphadenopathy, splenomegaly, fever and joint pains accompanied the bleeding episodes, the elevated antithrombin levels may well have been one manifestation of a general hypersensitivity reaction to the extravasated blood.<sup>10</sup> Protamine titration gave no evidence of the presence of heparin-like activity.

One of the problems in quantitation of coagulation defects and in evaluating treatment in this patient was the fluctuation in the severity of her disease. There was a close correlation between her bleeding

\* These determinations were kindly performed by Dr. Demetrios A. Rigas at the University of Oregon.

MAY, 1956

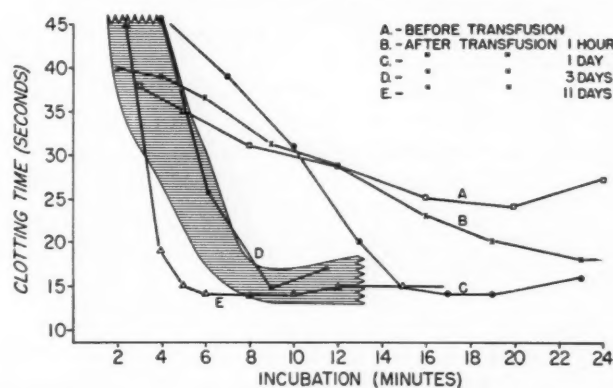


Fig. 3. Thromboplastin generation test (using patient's serum, normal plasma [BaSO<sub>4</sub>-adsorbed], normal platelets and CaCl<sub>2</sub>). Control determinations fell in shaded area.

were never so markedly prolonged and elevated antithrombin was not demonstrated. These differences would appear to be consistent with the improvement in the patient's general bleeding tendency at the later date. The Quick test showed results similar to those obtained previously, and this abnormality was found to reflect a depressed plasma content of both factor VII and prothrombin like that found in dicumarol plasma. (Fig. 2.) Factor V (labile factor, Ac-globulin) was always normal (80 to 110 per cent).

The thromboplastin generation test was normal, using barium sulfate-adsorbed plasma from the patient as a source of antihemophilic globulin, together with normal serum, normal platelets and CaCl<sub>2</sub>. When the patient's serum was combined with adsorbed normal plasma, normal platelets and CaCl<sub>2</sub>, an abnormal curve was noted. Not only was the incubation time required for the mixture to obtain maximum activity prolonged, but also the amount of activity measured never reached the normal range. (Fig. 3A.) Abnormal thromboplastin generation

TABLE IV

Experimental Conditions	Activity in Per cent		
	Prothrombin Complex Activity (Quick)	Prothrombin	Factor VII
A. <i>In vitro</i> incubation of plasma and purified prothrombin and factor VII:			
(a) Immediate.....	.....	66	51
(b) 24 hr.....	.....	66	61
B. <i>In vivo</i> effect of plasma:			
(a) Patient plasma before transfusion.....	9.5	19	5
(b) Immediately following transfusion.....	20	25	13.5
(c) Calculated content*.....	29	37	26.2

\* Calculations based on a plasma volume of 2,000 and administration of 575 ml. of fresh plasma containing 100 per cent prothrombin and factor VII.

curves are obtained both when the test serum employed is that from patients receiving dicumarol or from those with hemophilia B;<sup>11</sup> the type of curve obtained here resembles the first. (Fig. 4.) This has been explained by assuming the participation of factor VII in thromboplastin generation<sup>12</sup> but another hypothesis involves the role of factor X in producing this abnormality.<sup>13</sup>

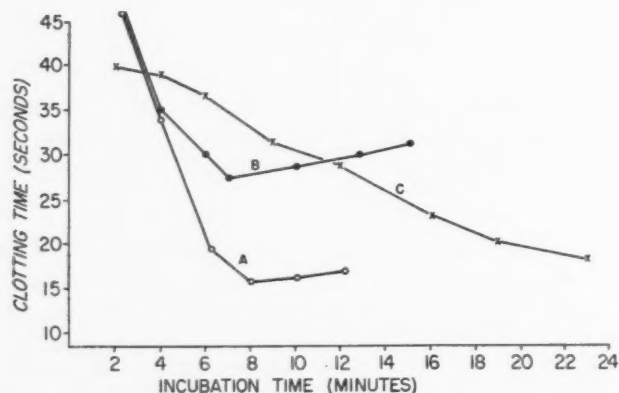


FIG. 4. Thromboplastin generation test was performed using normal BaSO<sub>4</sub>-adsorbed plasma, normal platelets, CaCl<sub>2</sub> and normal serum (A) hemophilia β serum, (B) serum of our patient or dicumarol serum (C).

**Response to Vitamin K and Derivatives.** The response to intravenous menadione (2-methyl 1,4-naphthoquinone) bisulfite has been demonstrated by brief and minor rises in prothrombin and factor VII. (Fig. 2.) Better responses have been obtained with very large doses of 2-methyl-3-phytyl-1,4-naphthoquinone (K<sub>1</sub>) given either intravenously or orally (Fig. 5); 1 or 2 gm. intravenously or 2 to 5 gm. orally per week were required to prevent serious hemorrhage. Even then the brief and variable response to vitamin

K and the development of what appeared to be resistance made this an unreliable form of therapy. Bleeding occasionally occurred despite its use.

**Effect of Plasma and Derivatives.** The defect in this plasma could be corrected *in vitro* by the addition of normal plasma. Thus when the patient's plasma with a prothrombin activity (Quick) of 25 per cent was employed, a 1:1 mixture with normal plasma resulted in an activity of 75 per cent. The defect was unaltered by the *in vitro* addition of dicumarol plasma. A 1:1 mixture of the patient's plasma with dicumarol plasma (prothrombin contents of 25 and 14 per cent, respectively) resulted in a prothrombin activity of 26 per cent. When normal plasma or a purified fraction containing prothrombin and factor VII\* was added to the patient's plasma in amounts sufficient to raise prothrombin and factor VII from 15 and 9.5 per cent, respectively, to nearly normal values and the mixture was allowed to stand at room temperature for twenty-four hours, the activity of these two factors remained constant. (Table IV, A.) There was therefore no *in vitro* evidence of a prothrombin-destroying substance.

Following a fresh plasma transfusion the immediate increase in concentration of prothrombin and factor VII was less than that calculated on the basis of dilution. (Table IV, B.) This discrepancy is similar in magnitude to that observed with transfusion of other plasma proteins and may be ascribed to the extravascular localization of a portion of the plasma.<sup>14</sup>

A more significant secondary increase in both prothrombin and factor VII occurred during the first three days after the plasma had been transfused. (Figs. 2 and 6.) It was necessary to inject a minimum of 300 to 400 cc. of plasma to produce this effect (about 20 per cent of the patient's plasma volume).

\* The fraction was obtained through the courtesy of Dr. Walter H. Seegers.



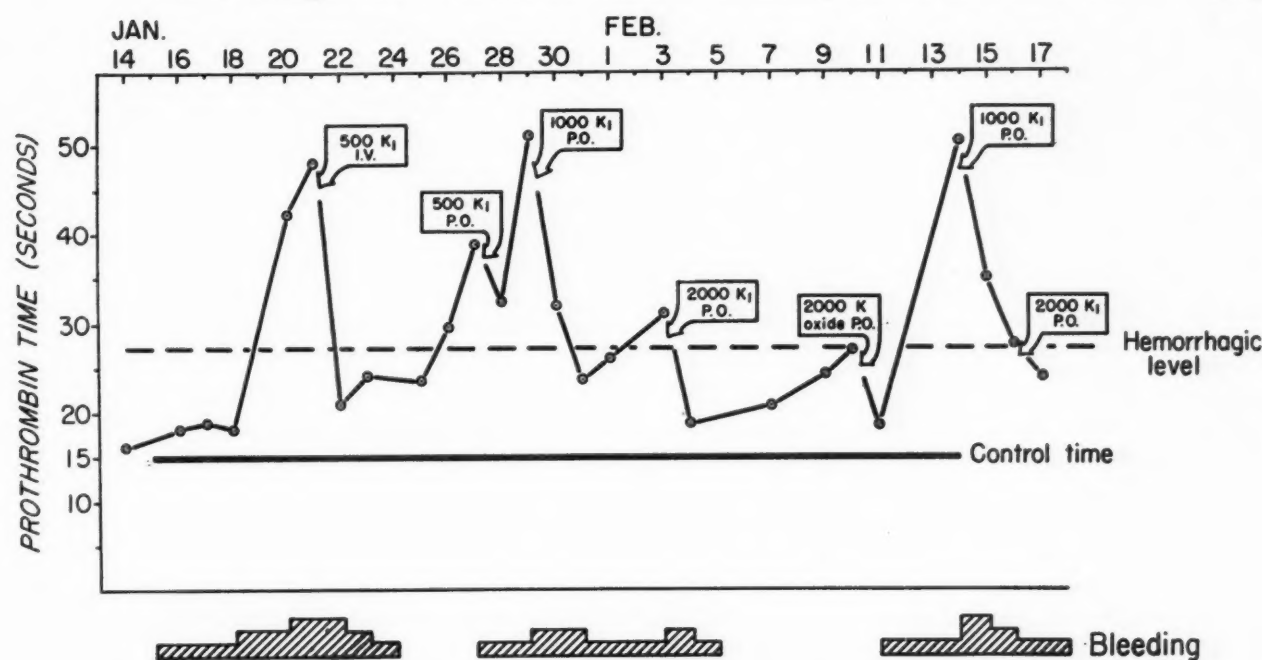


FIG. 5. Effect of vitamin  $K_1$  administration on bleeding and on prothrombin time in patient R. G.

Plasma refrigerated at  $4^\circ\text{C}$ . for two or more weeks, as well as frozen plasma, was unreliable in producing this effect. Fresh serum did not show the delayed response. (Fig. 6.) The thromboplastin generation test (Fig. 3) also did not reach normal until the third day post-transfusion, and improvement continued through the tenth post-transfusion day. The patient's plasma prothrombin activity remained normal for one to two weeks. Thereafter a progressive fall in prothrombin and factor VII occurred and was correlated with increasing abnormality in the thromboplastin generation test. The defect usually became severe enough to result in ecchymosis and other minor bleeding episodes between the third and fourth weeks if subsequent plasma transfusion was withheld.

#### DISCUSSION

Patterns of bleeding observed in various diatheses may be categorized clinically as manifesting predominantly petechial hemorrhage, focal "blow-out" hemorrhage or diffuse hemorrhage. The first may be produced by qualitative or quantitative deficiencies in platelets or by disturbances of the vascular integrity; the second by hemophilia, afibrinogenemia or circulating anticoagulants; the third by deficiencies of prothrombin and factor VII. The differences between these types of bleeding are well illustrated by their typical skin lesions. The pathognomonic finding in thrombocytopenia or vascular purpura is multiple pinpoint hemorrhages. In hemophilia a subcutaneous non-pigmented swelling is first observed, which is

followed some time later by the appearance of heme pigments. The more common clinical manifestations include hemarthrosis, epistaxis, hematuria and bleeding following tooth extrac-

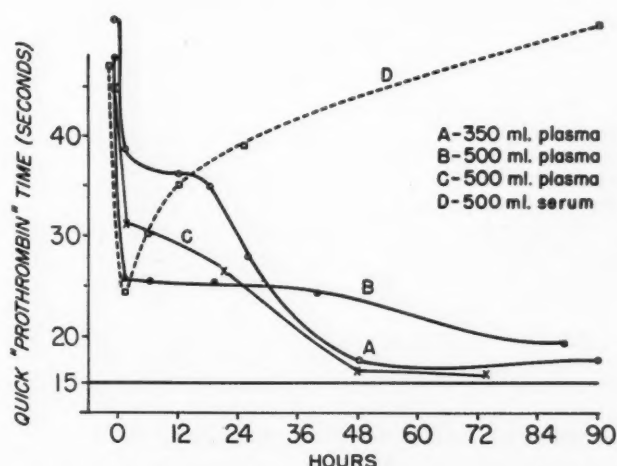


FIG. 6. Effect of transfused serum and fresh plasma on prothrombin time. An immediate effect was noted in each instance. However, fresh plasma resulted in continuing improvement. Lowest prothrombin time was usually reached at forty-eight to seventy-two hours and normal levels were maintained for ten to thirty days. Curves A, B and D were obtained in 1951, curve C in 1954.

tion. In hypoprothrombinemia, following cutaneous bleeding discoloration is immediately apparent in large areas. In this condition bleeding occurs in virtually all body tissues. Factor V

deficiency, appropriately called parahemophilia, results in hemorrhagic phenomena intermediate between the second and third categories. Here epistaxis and bleeding from teeth are quite common. Joint hemorrhage is less frequent but occurs more often than in factor VII—prothrombin deficiency. Pulmonary, intestinal and urinary bleeding are rare. The report of Koller<sup>15</sup> that factor V deficiency may be associated with a defect in hemophilia A factor further relates these two.

In the patient R. G. there was negligible petechial hemorrhage. In contrast to the bleeding in hemophilia, which originates from single loci, were the diffuse, often simultaneous hemorrhages seen here. These manifestations, including ecchymosis, epistaxis, hematemesis, hemoptysis, melena, hematuria and cerebral hemorrhage, were very similar to those observed with dicumarol intoxication. Laboratory demonstration of prothrombin and factor VII deficiencies corroborated this similarity.

Studies of the response to vitamin K therapy indicated that huge amounts (1 or 2 gm. intravenously) of vitamin K<sub>1</sub> were required to produce significant elevations of prothrombin and factor VII. These effects were limited to a one- to three-day period. It is difficult to compare the response of other patients with congenital abnormalities of the prothrombin complex to vitamin K<sub>1</sub> since the dosages employed were not of the size reported here. Most patients with such a congenital defect have been reported to respond poorly or not at all to vitamin K.

Although plasma has been reported to be temporarily effective in vitamin K-resistant patients, the delayed response to plasma observed in this patient is, to our knowledge, unique. This response consisted of a primary increment due to the transfused prothrombin and factor VII, followed by a secondary generation of prothrombin and factor VII over a period of three days to normal levels. These normal levels were maintained for a period of seven to fourteen days. Since transfused prothrombin,<sup>16</sup> factor V<sup>17</sup> and factor VII<sup>18</sup> persist over only a one- to three-day period, the effect cannot be ascribed to simple replacement of these deficiencies.

In considering the nature of this prothrombin-factor VII abnormality, any dietary or absorptive abnormality relating to vitamin K metabolism can be excluded because of the impaired response to parenteral vitamin K. There was no

clinical evidence of liver disease and repeated liver function tests were normal. The fact that response did occur to large doses of vitamin K must indicate either a block in synthesis which was temporarily and partially overcome, or that these coagulation factors are subject to rapid destruction and that massive doses of vitamin K were effective by further accelerating production. We suggest as the most attractive possibility that this patient, through a congenital metabolic defect, lacks some essential substance which is required in common to the production of prothrombin, factor VII and perhaps factor X. It is of interest to speculate as to whether this might be a structural analog of these compounds, an enzyme involved in synthesis or an apoenzyme to vitamin K. The possibilities further exist that there might be an inhibiting substance neutralized by the transfused plasma, or that a physiologic prothrombolytic mechanism in this patient may not have a normally present antagonist which is supplied by plasma transfusion. Whatever the mechanism, it could not be defined by *in vitro* tests. The factor involved may deteriorate under refrigeration conditions and appears to be used up in the coagulation process since fresh serum is ineffective. Large amounts of fresh plasma are necessary if the effect is to be produced, and the *in vivo* duration of the effect extends over a ten- to twenty-day period.

#### SUMMARY

A detailed study is presented of a thirty-two year old woman with a congenital deficiency of prothrombin and factor VII. The defect found is similar to that of (acquired) dicumarol toxicity and involves thromboplastin generation as well as the prothrombin complex.

This deficiency has caused recurrent severe hemorrhages, the nature of which distinguishes this disorder clinically from other hemorrhagic diatheses. Response to vitamin K and its derivatives was poor. Monthly treatment with fresh plasma transfusions was effective in controlling bleeding over a four-year period.

The delayed and prolonged *in vivo* response of prothrombin and factor VII to fresh plasma observed in this case is unique. Its mechanism is as yet unexplained.

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# Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism\*

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IT is well known that thrombocytopenic purpura may be caused by drugs and chemical agents. In the case of sedormid,<sup>®1-7</sup> quinine<sup>8</sup> and quinidine<sup>9-12</sup> *in vitro* technics have been devised which suggest that an immune mechanism is responsible for the thrombocytopenia and capillary alterations which result from sensitivity to the drug. The reaction apparently responsible for drug-induced thrombocytopenia is of interest in that a fourth factor (the drug) is required in addition to the usual three factors (antigen, antibody and complement) involved in a lytic reaction.<sup>6</sup>

A case is presented in which hemolytic anemia as well as thrombocytopenic purpura occurred following the administration of quinidine. To our knowledge, hemolytic anemia due to quinidine has not been previously reported. Moreover, prior to a report in the recent literature<sup>30</sup> of hemolysis secondary to fuadin<sup>®</sup> administration, a specific immune mechanism had not been previously demonstrated in any drug-induced hemolytic anemia. It is for these reasons and because of the considerable theoretic importance of this mechanism that we present a case of quinidine-induced hemolytic anemia and thrombocytopenic purpura with observations supporting the concept that an immunohematologic process is responsible.

## CASE REPORT†

A sixty-nine year old white man (No. 66465) entered Montefiore Hospital for the second time on October 31, 1954, because of palpitations of one day's duration. For the previous two years the patient had experienced several mild episodes of transient palpitations for which he had taken tablets of quinidine sulfate. On the day of admission he had persistent palpitations and was referred to the hospital. The significant past history included a primary syphilitic

infection of the pharynx at fifteen years of age (treponema immobilization test positive), a known heart murmur for fifteen years with no history of rheumatic fever and two episodes of coronary occlusion with myocardial infarction.

Physical examination on admission revealed a well nourished and well developed white man. Temperature was 98.6°F., pulse 120 and irregular, blood pressure 120/60, and respirations 16. The examination, aside from the heart, was within normal limits except for a large defect in the palate and right side of the uvula. The heart was not enlarged. The second pulmonic sound was louder than the second aortic sound. There was a grade II blowing systolic murmur and rumbling diastolic murmur at the apex. The rhythm was totally irregular. The clinical impression was rheumatic and arteriosclerotic heart disease with mitral stenosis, mitral insufficiency and paroxysmal supraventricular tachycardia. Electrocardiograms revealed a supraventricular tachycardia with intermittent bundle branch block and aberrant conduction.

The patient was given cedilanid followed by digoxin.<sup>®</sup> When this failed to break the arrhythmia he received 2.6 gm. of quinidine sulfate by mouth on the first day, 2.4 gm. on the second day and 0.8 gm. on the third day for a total of 5.8 gm. By the second hospital day the rhythm was nodal and then reverted to regular sinus rhythm. The patient was given a maintenance dose of 0.2 gm. of quinidine every six hours. On the fourth hospital day a purpuric eruption was noted on the arms, legs and trunk, and the quinidine was stopped promptly. For the next four days the patient received intramuscular ACTH, 40 units a day. The patient had a temperature of 101 to 102°F. for the first three days. Digoxin was stopped on the fourth day. There was one episode of epistaxis on the day of the purpura but no evidence of other bleeding. At this time the platelets were almost completely absent in stained blood smears, the clotting time was eight minutes and clot retraction was absent after twenty-four hours. A Rumpel-Leede tourniquet test was strongly positive.

A sternal bone marrow aspiration taken on November 5, 1954, revealed marked erythroid hyperplasia and an increased number of megakaryocytes which showed a striking absence of platelet production.

† The authors wish to express their appreciation to Dr. Alter Weiss for his permission to study this patient.

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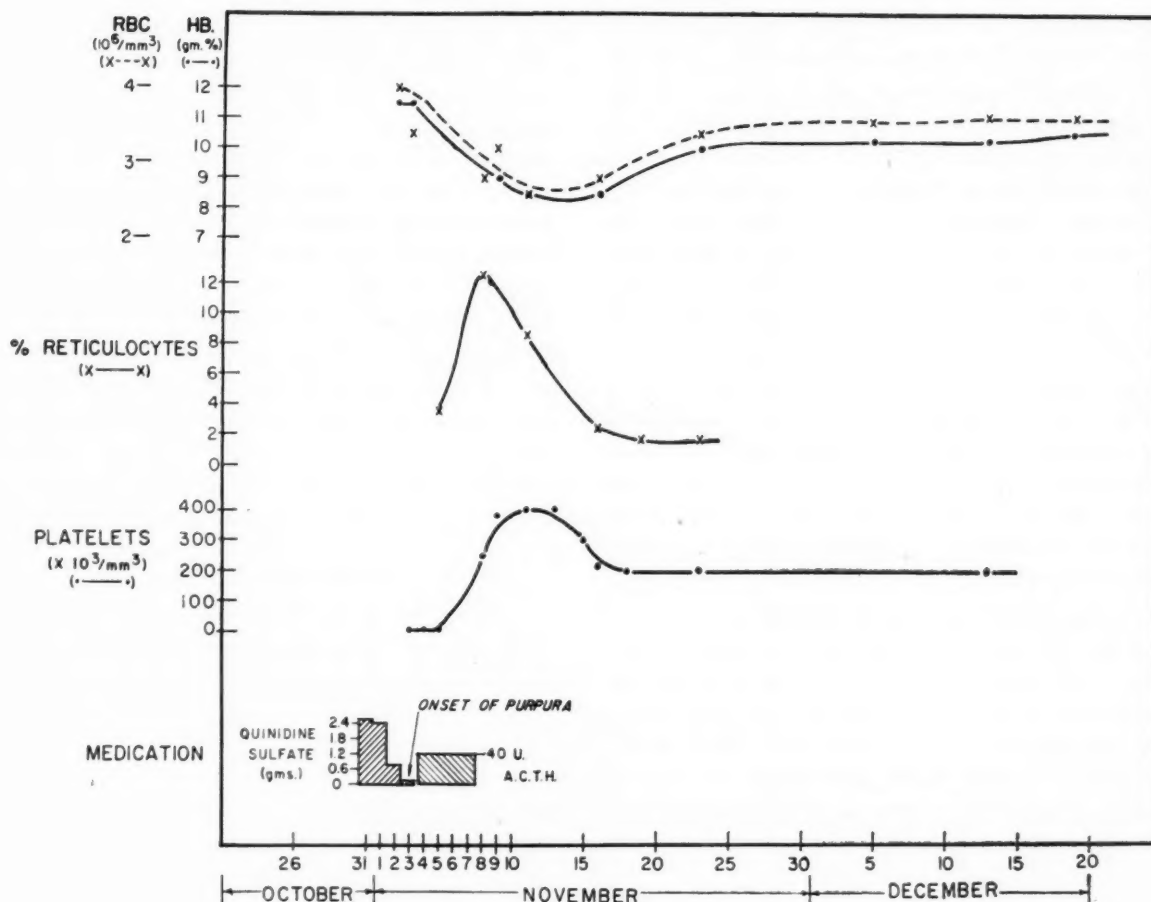


FIG. 1. Graphic representation of hematologic course.

Peripheral blood smears from November 3rd through November 13th exhibited schizocytes, spherocytes, 0 to 2 per cent normoblasts and progressive basophilic macrocytosis reaching its peak on November 8th. The hematologic data (Fig. 1) clearly suggested a hemolytic anemia in addition to thrombocytopenic purpura. During this period the leukocyte count ranged between 5,000 and 10,000 per cu. mm. The differential count on November 3rd, when the white blood cell count was 8,250 per cu. mm., showed 63 polymorphonuclears, 20 stab forms, 3 metamyelocytes, 9 lymphocytes and 5 monocytes. From November 4th through November 12th a plasmacytosis (1 to 5 per cent) was noted in association with atypical mononuclear cells (? atypical plasma cells).

The serum bilirubin measured 0.4 and 0.5 mg. per cent on November 5th and 9th, respectively; one month later it was 0.26 mg. per cent. Fasting blood sugar was 77 mg. per cent, blood urea nitrogen 18 mg. per cent, serum albumin and globulin 4.0 and 2.5 gm. per cent, respectively. Routine urinalyses were unremarkable. The Coombs test (direct, indirect and trypsin-treated) was negative on two occasions. Cold agglutinins could not be demonstrated and a Donath-Landsteiner test was negative. Suitable preparations failed to show erythrophagocytosis or lupus erythematosus cells.

MAY, 1956

By the sixth hospital day the purpura had subsided considerably and was completely gone in the next two days. There was no recurrence. Thrombophlebitis developed which was treated with dicumarol for eleven days. Subsequently, the course was further complicated by spiking fever to 101°F. Despite the absence of classic findings of subacute bacterial endocarditis and despite repeatedly negative blood cultures, a course of penicillin therapy for subacute bacterial endocarditis was given. There was one other episode of paroxysmal supraventricular tachycardia which was treated with redigitalization after which the rhythm became fixed in auricular fibrillation. The rate was controlled with maintenance doses of digoxin and the patient was discharged from the hospital.

## SPECIAL STUDIES

During the recovery phase from thrombocytopenic purpura we attempted, as have other investigators,<sup>1-4,10,11</sup> to demonstrate that clot retraction was impaired by the addition of small amounts of the suspected drug to the patient's blood. In the course of following the clot retraction it was noticed that hemolysis was present in the tube containing the patient's blood plus

quinidine whereas it was absent in tubes containing the patient's blood plus quinine, the patient's blood plus saline solution, and control bloods plus quinidine, quinine or saline solution. The following experiments were carried out for further study of this hemolytic phenomenon.\*

**Materials.** *Red blood cell suspensions:* Five per cent suspensions of human erythrocytes were made in 0.9 gm. per cent saline solution using cells washed three times. The suspensions were used within six hours of venepuncture.

*Serum and plasma:* A wide variety of serums and plasmas was employed. They were obtained from oxalated blood, sequestrenated blood,† heparinized blood, defibrinated blood and clotted blood. Control samples were used within six hours of venepuncture. The patient's samples were employed on the day of venepuncture except where otherwise specified.

*Complement:* Fresh human serum, fresh rabbit serum, and fresh and lyophilized guinea pig serums were used as the source of complement. When necessary, inactivation was effected by heating to 57°C. for thirty minutes.

*Drugs:* The various agents employed, except when otherwise specified, were made up in 0.9 gm. per cent saline solution.

*Coombs antiserum:* A supply of potent anti-human globulin rabbit serum was used.

*Amboceptor:* A commercially available potent anti-sheep cell rabbit serum was employed.

*Suspension of sheep red blood cells (washed three times):* Fresh sheep erythrocytes were made up in 2 per cent suspension with 0.9 gm. per cent saline solution and used on the same day.

*Control Patients.* Control subjects were selected at random from among a large number of medical and surgical cases at the Montefiore Hospital. As will be indicated, some had previously been and some still were receiving quinidine therapy. Three were in the recovery phase of quinidine-induced thrombocytopenic purpura without hemolytic anemia. The great majority of control subjects were of blood groups compatible with that of the patient (O, Rh positive).

*General Procedure.* Special technics will be described in their appropriate places. In the majority of experiments equal parts (usually

0.1 ml.) of the various materials were employed. The basic experimental procedure involved a serologic test tube in which the following were serially added: (1) erythrocyte suspension, (2) drug, (3) serum or plasma, and (4) complement. The test tubes were carefully shaken and incubated for forty-five minutes at 37.5°C. Following incubation they were rapidly centrifuged and the contents examined for hemolysis and hemagglutination. Relative amounts of hemolysis were easily appreciated visually and recorded on an arbitrary scale from 0 to 4+. Agglutination was read by the technic of test tube rotation and gradations from 0 to 4+ were easily and reproducibly read. The readers were not aware of the contents of the tubes examined.

#### EXPERIMENTAL DATA

*Titration of Serum Hemolytic Factor in Relation to Time Interval Since the Clinical Hemolytic Reaction.* As may be seen in Figure 2, the patient's serum was periodically examined for antibody activity. Equal parts of a compatible 5 per cent erythrocyte suspension, 30 mg. per cent quinidine sulfate in saline solution, human complement and the patient's serum in serial twofold dilutions were used. Control serums, saline solution and inactivated human serum were used as controls for antibody, quinidine and complement, respectively. The titer of the hemolytic factor is expressed as *final titer*, i.e., the reciprocal of the *final* dilution of serum in the last tube that shows definite hemolysis. Hemagglutination was usually present through two tubes beyond the limits of hemolysis. It will be noted that the initial titer of 256 decreased three- to fourfold during the period (142 days) of observation, and that the titer remained relatively stable during the last 100 days of this period.

*Relation of Quinidine Sulfate Concentration to Hemolysis.* Figure 3 demonstrates that maximal hemolysis was obtained at a final concentration of quinidine sulfate ranging from 3.75 to 66 mg. per cent (the highest concentration tested) and that hemolysis was still distinctly present at a concentration of 0.375 mg. per cent although it was absent at a concentration of 0.188 mg. per cent. That these concentrations are pharmacologically effective is known from the data of Yount et al.<sup>13</sup> which indicate that therapeutic serum levels of quinidine range roughly from 0.2 to 2.0 mg. per cent (which correspond to quinidine sulfate levels of 0.24 to 2.4 mg. per cent). An average level of 0.91 mg. per cent quinidine

\* Special studies relating to the mechanism of quinidine-induced thrombocytopenic purpura in four cases will be presented in a later communication.<sup>28</sup> In only one (the present case) was hemolytic anemia present clinically and capable of the *in vitro* demonstration described here.

† Blood treated with sequestrene.



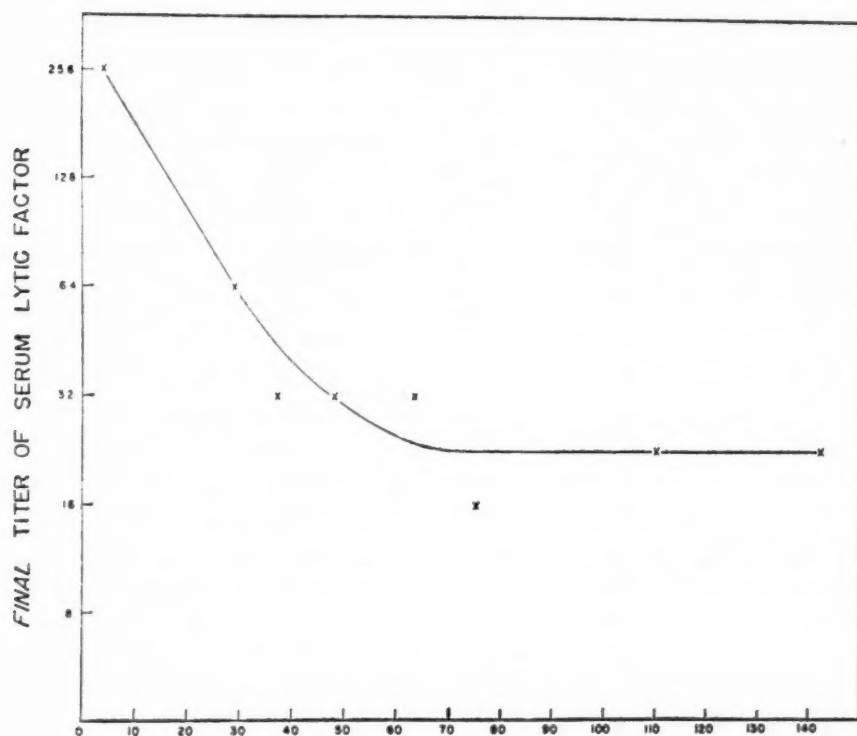


FIG. 2. Duration of potency of serum hemolytic factor. Days after appearance of purpura and hemolysis.

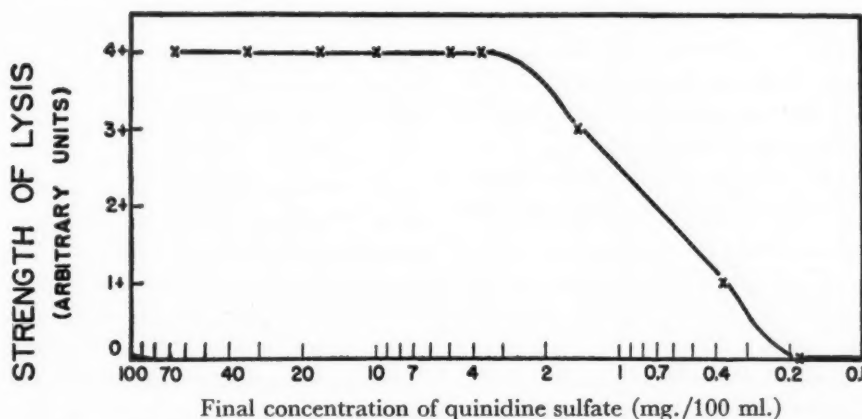


FIG. 3. Relation of quinidine sulfate concentration to hemolytic activity.

base (1.19 mg. per cent quinidine sulfate) was obtained after oral administration of 0.42 gm. quinidine sulfate every four hours.

To show directly that the blood levels of quinidine after ordinary therapeutic dosage were sufficient to activate the hemolytic system, several control patients were given quinidine sulfate orally, 0.4 gm. every three hours for four doses, and serum was obtained one hour following the last dose. Table I shows that sufficient quinidine concentration was obtained to produce hemolysis in the presence of antibody, complement and erythrocytes when the final quinidine concentrations reached in the test tubes were at least

one-half to two-thirds of the levels reached in the serums (dilution by the saline solution, erythrocyte suspension, patient's serum).

*Antibody and Erythrocyte Controls.* In order to demonstrate that the hemolytic mechanism was specific for the patient's serum and independent of the erythrocytes employed, we tested a large number of human control sources for serum and erythrocytes. A number of patients who were receiving or had recently received quinidine medication, including three recuperating from quinidine-induced thrombocytopenic purpura,\* were also used as sources of serum and erythrocytes.

\* See footnote, page 808.

TABLE I  
DEMONSTRATION THAT SERUM CONCENTRATIONS  
OF QUINIDINE SULFATE ORDINARILY ATTAINED  
MAY BE SUFFICIENT TO ACTIVATE  
THE HEMOLYTIC SYSTEM

0 + Red Cell Suspension (0.1 ml.)	NaCl Solution, 0.9 Per cent (0.1 ml.)	Patient's Serum (0.1 ml.)	Fresh Control "Quinidinized" Serum†	Final Dilution "Quinidinized" Serum	Lysis
X	—	X	A 0.1 ml.	$\frac{1}{8}$	0
X	—	X	A 0.2 ml.	$\frac{1}{4}$	+
X	—	X	B 0.1 ml.	$\frac{1}{8}$	0
X*	—	X	B 0.1 ml.	$\frac{1}{8}$	+
X*	X	—	B 0.1 ml.	$\frac{1}{8}$	0
X	—	X	C 0.1 ml.	$\frac{1}{8}$	0
X	—	X	D 0.1 ml.	$\frac{1}{8}$	0
X	—	X	E 0.1 ml.	$\frac{1}{8}$	0

\* Red cells suspended in B's "Quinidinized" serum.

† Serum from five control patients (A to E) receiving quinidine sulfate, 0.4 gm., every three hours for four doses and drawn one hour after the last dose.

The controls employed were patients with acute or chronic medical and surgical disease. Table II lists the various controls numerically. None of the control serums lysed the patient's or other compatible erythrocytes in the presence of quinidine and complement. All of the control erythrocytes could be lysed by the patient's serum in the presence of quinidine and complement. The antibody described in this report could not be related to the ABO or Rh isoantigens.

*Drug Controls.* All drugs which the patient received during the week prior to the appear-

TABLE II  
ENUMERATION OF RED CELL AND SERUM CONTROLS

I. Red cell controls	
O+.....	28
O-.....	2
A+.....	2
B+.....	1
AB+.....	1
Total	34
A. Obtained from patients receiving quinidine	
1. Without reaction.....	6
2. With reaction*.....	3
II. Serum controls	
O+.....	30
O-.....	2
A+.....	2
B+.....	1
AB+.....	1
Total	36
A. Obtained from patients receiving quinidine	
1. Without reaction.....	6
2. With reaction*.....	3

\* Thrombocytopenic purpura.

TABLE III  
DRUG CONTROLS

Drug Employed*	Final Concentration (mg. %)	Lysis
Quinidine sulfate.....	5.00	++++
Quinidine hydrochloride...	5.00	++++
Quinine sulfate.....	5.00	0
Procaine amide.....	5.00	0
Digoxin.....	0.005	0
Cedilanid.....	0.003	0
Testosterone propionate....	1.25	0
Hydrocortisone.....	2.50	0
Hydrocortisone.....	1.25	0
Hydrocortisone with.....	2.50	++++
quinidine sulfate.....	5.00	

\* In presence of red cells, patient's serum and complement.

ance of the hemolytic reaction were tested as quinidine controls and to exclude a second causal agent. Quinine was tested to show stereoisomeric specificity, the usual finding in drug sensitivity.<sup>14</sup> All these drugs were ineffective in inducing lysis unless quinidine was present. Hydrocortisone was employed to determine whether it could block the hemolytic reaction *in vitro*. The degree of quinidine-induced lysis was not reduced by the addition of hydrocortisone. (Table III.)

*Characteristics of the Serum Hemolytic Factor* (Table IV). *Stability:* When the patient's serum was heated to 57°C. for thirty minutes no detectable loss of hemolytic activity was evident in the standard system. Heating to 60°C. for thirty minutes destroyed practically all hemagglutinating and hemolytic activity. Essentially full hemolytic ac-

TABLE IV  
CHARACTERISTICS OF THE HEMAGGLUTININ AND HEMOLYSIN

1. Stable
  - At 25°C. for over 14 days
  - At -20°C. for over 100 days
  - Resists heating to 57°C. for 30 minutes
  - Inactivated at 60°C. in 30 minutes
2. Activity not specifically influenced by incubation at a temperature range from 4°C. to 37°C.
3. Requires presence of quinidine
4. Potent in high dilution
5. Active against all red cells tested
6. Adsorbable on red cells in presence of quinidine
7. Causes hemagglutination in absence of complement and hemolysis as well in presence of complement
8. Migrates electrophoretically with gamma globulin
9. Fixes complement
10. Union with red cells and quinidine very loose; Coombs test, negative

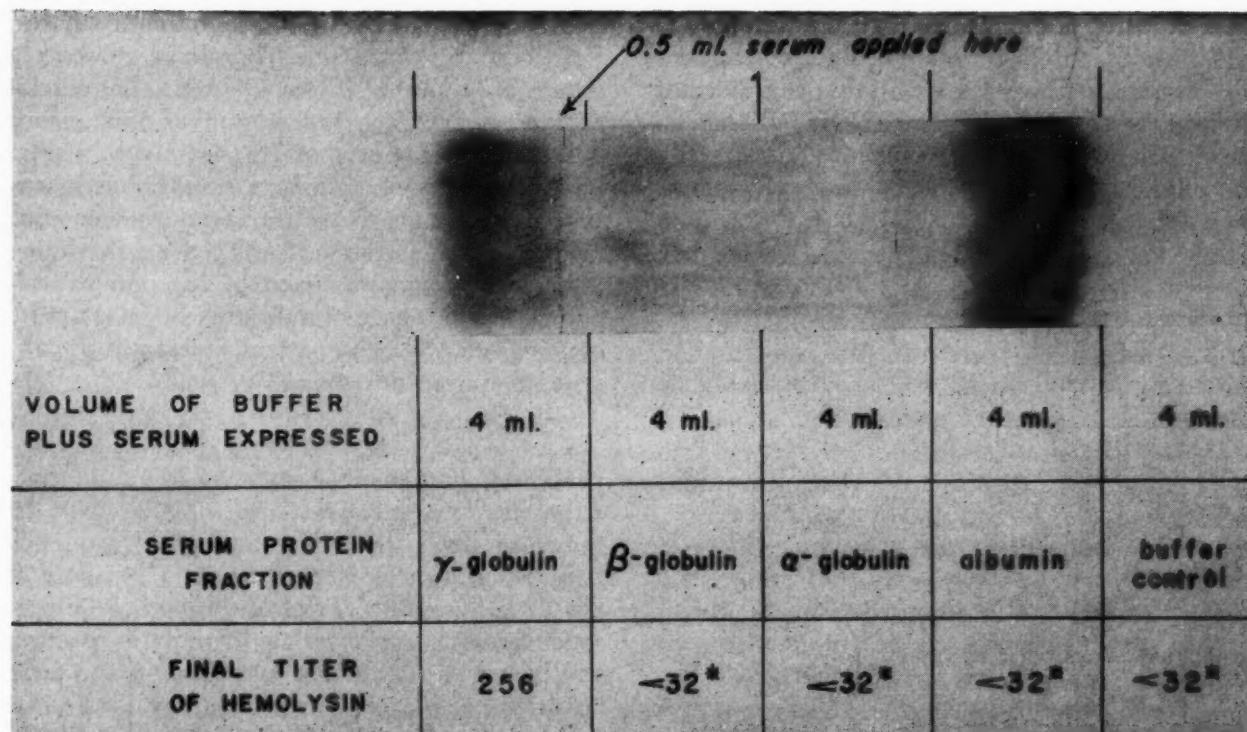


FIG. 4. Scheme of electrophoretic separation, and titration, of serum proteins. (See text.) Asterisk indicates that no hemolytic activity could be demonstrated in fractions other than gamma globulin. By the method employed, dilutions of less than 1:32 were not possible.

tivity was retained by the patient's serum stored at 25°C. for fourteen days and aged at -20°C. for more than 100 days.

**Hemagglutination:** This occurred equally well at 4°C., 25°C. and 37°C. Hemolysis was somewhat accelerated at the higher incubation temperatures. The factor present could not be properly classified either as "warm" or "cold."

**Paper electrophoresis:**\* This was performed by a modification of the Kunkel and Slater technic.<sup>16</sup> Separation of 0.5 ml. of the original high titer (1:256) serum was obtained by using thick absorbent filter paper (Eaton-Dikeman No. 320) suspended between glass plates from troughs containing veronal buffer at pH 8.56. A current of 6 ma. was drawn by 175 volts and satisfactory separation was obtained after twenty-three hours.

Brief apposition of a strip of Whatman No. 1 filter paper to the original strip provided a "daughter" strip which could be stained for protein without disturbing the original separation. The latter procedure permitted identification of the protein fractions which were then isolated

\* We are indebted to Dr. Bernard Sachs for assistance and advice in carrying out this portion of the investigation.

by cutting the thick filter paper and manually expressing the contents (buffer plus serum fraction) of each filter paper block into test tubes. Approximately 4 ml. of fluid were expressed from each block so that we may calculate that there was 1:8 dilution of each serum protein fraction of the original 0.5 ml. The various fractions isolated in this manner were serially diluted with saline solution and tested in the standard hemolytic system. Figure 4 illustrates the separation of the serum protein fractions and the hemolytic titer of each expressed as a *final* titer. Neither hemolysis nor hemagglutination occurred in any except the gamma globulin fraction and the expected titer was demonstrated there.

**Adsorption of Serum Factor.** By reacting the patient's serum (heated to 56°C. for thirty minutes) with an approximately equal volume of packed erythrocytes in the presence of quinidine it could be shown that the hemagglutinating activity of the supernatant against packed erythrocytes was lost after two passages. This activity could be restored by further addition of the patient's serum, thus supporting the concept that the hemagglutinin was adsorbable.

**Role of Complement.** Evidence was gathered in a number of experiments which indicates that,



as is expected of immune lytic reactions, complement is required for the *in vitro* quinidine-induced hemolysis described herein and that complement is fixed in the course of the reaction. Similar conclusions were reached by Ackroyd<sup>4-6</sup> and others<sup>11</sup> in relation to drug-induced thrombocytolysis.

TABLE V  
RELATIONSHIP OF HEMAGGLUTINATING AND HEMOLYTIC  
ACTIVITY TO COMPLEMENTARY ACTIVITY

Source and Treatment of Patient's Antibody	Agglutination	Lysis
Fresh serum.....	+	+
Fresh defibrinated serum.....	+	+
Fresh oxalated plasma.....	+	0
Fresh sequestrenated plasma.....	+	0
Fresh heparinized plasma.....	+	0
Fresh serum inactivated by:		
Heat (56°C. for 30 min.).....	+	0
Addition of sequestrene.....	+	0
Addition of oxalate.....	+	0
Serum obtained by:		
Recalcification of fresh sequestrenated plasma.....	+	+
Thrombinization of fresh sequestrenated plasma.....	+	0
Complement added to heat-inactivated serum:		
Fresh control human serum.....	+	+
Fresh rabbit serum.....	+	+
Fresh guinea pig serum.....	+	+
Lyophilized guinea pig serum.....	+	+

Some investigators<sup>12</sup> have been unable to demonstrate thrombocytolysis and the need for complement, perhaps because of excessive anticoagulation and inadequate addition of complement.

As shown in Table v, *hemagglutination* was induced by any form of the patient's serum or plasma as long as quinidine was present. *Hemolysis*, however, occurred only when sufficient complementary activity was present. It is known that oxalate, sequestrene and heparin may be anticomplementary and that this effect can be overcome in the first two instances by recalcification. (Table v.)

The minimal concentration of human complement required to produce lysis was in the range of 1:12 (final dilution 1:48). Fresh rabbit serum and one sample of fresh guinea pig serum showed higher complementary activity. Lyophilized guinea pig serum exhibited much lower com-

plementary activity in this reaction than did fresh human serum. The lyophilized guinea pig serum obtained from two different commercial sources was reassayed on a number of occasions with the same poor showing of activity, a phenomenon for which we have no satisfactory explanation. By the use of the standard sheep red cell-amboceptor system it was repeatedly shown that complement was fixed by the patient's serum in the presence of quinidine but not by the control sera or by the patient's serum in the absence of quinidine.

#### COMMENTS

Hemolytic anemia has been frequently attributed to a number of drugs and chemicals. In many instances the cause and effect sequence has not been proved by means of a test dose of the drug after subsidence of the hemolytic episode. In other instances the hemolytic reaction can be attributed to processes unrelated to drug sensitivity. Thus, as pointed out by Dacie,<sup>16</sup> a number of patients<sup>17-19</sup> in whom hemolysis developed in relationship to sulfonamide medication would appear to have had viral pneumonias with cold agglutinins and hemolysis due to the primary disease rather than to the medications. Nevertheless, it seems reasonable to accept a number of drugs as capable of producing hemolytic anemia. These are arranged categorically in the paragraphs that follow.

*Drugs Causing Hemolysis by a More or Less Direct Action on Erythrocytes.* Certain agents produce hemolysis regularly and in relation to dosage. These may act in the form of the parent compound or through metabolic products with significant hemolytic activity. In this category fall<sup>16</sup> phenylhydrazine, acetylphenylhydrazine, naphthalene,  $\beta$ -naphthol, trinitrotoluene, benzene, nitrobenzene, acetanilide, phenacetin, promin, arsine, lead, and probably phenothiazine, phenylsemicarbazide (cryogenine) and the sulfonamides. It has been shown<sup>20</sup> that naphthalene mothballs cause hemolysis *in vitro* and *in vivo* both through the weak action of the original compound and also through the stronger action of its metabolites ( $\alpha$ -naphthol,  $\beta$ -naphthol,  $\alpha$ - and  $\beta$ -naphthoquinone). It has also been shown<sup>21</sup> that the sulfonamides may produce hemolysis by the direct lytic activity of certain of their metabolites which can act as oxidants in oxidation-reduction systems (e.g., para-aminophenol and phenylhydroxylamine) although the original substance shows none of this activity *in vitro*.

*Anti-malarial agents of the 8-aminoquinoline group:*

Certain agents of this group appear to produce hemolytic anemia in a direct manner although at first glance they behave capriciously. As has been clearly shown by Dern et al.,<sup>22</sup> primaquine produces hemolysis in susceptible Negroes by a direct effect on cells. The susceptibility of certain erythrocytes seems to depend on genetic and enzymatic factors. Thus Cr<sup>51</sup>-labelled red cells from a susceptible individual injected into a normal recipient are selectively lysed when the recipient is given primaquine and, conversely, normal tagged red cells are unaffected when a susceptible recipient receives primaquine.

*Drugs Causing Hemolysis due to "Hypersensitivity" (i.e., Immuno-hemolytic Anemia).* Although sulfonamides may be responsible for hemolytic anemia in some cases through direct effects of some of their metabolites, as already noted, there is no question<sup>16,23</sup> that they are capable of, and not infrequently do, cause hemolysis on the basis of "hypersensitivity." As opposed to the direct mechanism which produces hemolysis more slowly and in relation to dosage, the hypersensitive mechanism produces an acute picture, unrelated to dosage, with onset usually one to three days following the start of sulfonamide therapy. It has been noted that readministration of the agent reproduces the hemolytic anemia in susceptible individuals.<sup>23</sup> Aside from reactions produced by sulfanilamide and sulfapyridine, acute hemolytic episodes due to sulfonamides are rare. In no instance has the hypersensitivity postulate been further defined, and the occasional reports of abnormal antibodies (e.g., cold agglutinins) can be more fairly ascribed to the primary illness than to the medication.

In a number of instances quinine taken in large doses as an abortifacient has probably been responsible for hemolysis.<sup>16,24</sup> In no case, to our knowledge, was a test dose administered or *in vitro* data collected to substantiate the relationship. Evidence exists which suggests that quinine may facilitate hemolysis by a direct (non-immune) mechanism, as noted in the review of Licciardella and Stanbury.<sup>24</sup> Similarly, although there are hypotheses<sup>16,25</sup> concerning the role of quinine in initiating the hemoglobinuric syndrome of blackwater fever no data are available which fully establish the pathologic physiology and immunology of this process.

The relationship of other agents to hemolytic anemia on an immune basis is conjectural<sup>16</sup> although a few cases have been ascribed to

para-aminosalicylic acid and rare cases to neoarsphenamine, mesantoin,<sup>26</sup> antihistaminics and d,l-amphetamine. In none of these is the relationship clear since test doses were never employed and *in vitro* technics of the sort herein described were not utilized.

Recently, a case of hemolytic anemia following the administration of fuadin was reported in which a serum factor was present that caused *in vitro* agglutination (but not hemolysis) of the patient's red blood cells or normal red blood cells, rendered these cells Coombs-positive and had a high initial titer which fell progressively over a sixty-day period.<sup>30</sup> These reactions occurred only in the presence of fuadin.

Although proof that an immunohematologic mechanism may be responsible for a drug-induced hemolytic anemia was previously lacking, proof of an immunothrombolytic cause for thrombocytopenic purpura due to drugs has been provided repeatedly over the past seven years. In 1948 Grandjean<sup>8</sup> demonstrated that addition of quinine to the blood of a patient convalescing from thrombocytopenic purpura, presumably induced by quinine, produced a fall in the platelet count *in vitro* and that the responsible serum factor persisted in the patient's blood for at least three months. In the same year Ackroyd<sup>2</sup> subjected several cases of sedormid-induced thrombocytopenic purpura to analysis and was able to demonstrate in succeeding years<sup>1-7</sup> that the serum of these patients contained a factor which agglutinated platelets in the absence of complement; lysed platelets in the presence of complement and fixed complement in the process; required the presence of sedormid for these effects; and whose behavior is in essence that of an antibody. Bigelow and Desforges<sup>9</sup> demonstrated similar *in vitro* phenomena in two cases of quinidine-induced thrombocytopenic purpura and since that time a number of cases with similar *in vitro* findings have been reported.<sup>10-12</sup>

Leukopenia due to drugs has been commonly described but *in vitro* demonstration of the role of the presumably responsible agent remains to be shown, although leukagglutinins not requiring the presence of the presumed causal drug for activity *in vitro* have been demonstrated in leukopenia due to (or associated with) pyrimidon.<sup>27</sup>

It is of more than passing interest that the present case demonstrated thrombocytopenic purpura as well as hemolytic anemia. As will be described at a later date,<sup>28</sup> the immune patho-



genesis of both these processes has been established in this patient by *in vitro* and other special procedures. Evans et al.<sup>29</sup> and others<sup>16,25</sup> have pointed out the frequent coexistence of immunocytopenias of the idiopathic variety. Thus in one series<sup>29</sup> approximately 50 per cent of patients with idiopathic acquired hemolytic anemia had thrombocytopenia, and approximately 65 per cent of patients with idiopathic thrombocytopenic purpura had hemolytic anemia or a positive Coombs test. It is clear that the present case fits into what Dameshek<sup>25</sup> has termed Evans' syndrome, including as it does immunothrombocytopenic purpura and immunohemolytic anemia.

**Mechanism.** As suggested by others,<sup>1,16,25</sup> drug-induced immunocytopenias may be mediated by the responsible agent in some manner rendering the cell antigenic either by (1) directly damaging and so altering the cell that it becomes "foreign" and antigenic or (2) attaching to the cell as a hapten in which case not only the red blood cell and antibody but also the drug (hapten) must be present at a later date for demonstration of the immunocytologic reaction.

In the present case it has been possible to demonstrate the necessity for the presence of the offending drug for the production of *in vitro* hemagglutination and hemolysis, thus supporting the second hypothesis. Ackroyd,<sup>7</sup> in his study of the mechanism of sedormid thrombocytopenia, measured complement fixation as an index of the occurrence of an *in vitro* immunothrombolytic reaction and demonstrated that the union of antigen (platelet), antibody and 'hapten' (sedormid) was extremely unstable. Thus when platelets were washed three times in saline solution after being reacted with the serum factor plus sedormid and prior to the addition of complement, complement fixation failed to occur. Dialysis of the mixture similarly blocked complement fixation. Only when the treated platelets were washed in sedormid instead of saline solution could complement fixation be demonstrated. Ackroyd concluded that sedormid acts in this reaction as a hapten which binds, in an extremely loose manner, the platelet to the antibody.

We studied the relation of red cells, antibody and quinidine in a similar manner using agglutination and lysis rather than complement fixation as the end point, since this could be very reliably measured for red cells although not for platelets. When red cells were washed in saline

solution after reaction with antibody and quinidine, agglutination was abolished and lysis could not be effected by later addition of complement, complement plus antibody, or complement plus quinidine. When the red cells were washed in quinidine solution after reaction with antibody and quinidine, similar negative results were obtained. The lack of stability of the antigen-antibody-hapten combination was also demonstrated by the Coombs test. Potent antihuman globulin rabbit serum failed to agglutinate erythrocytes which were washed in the usual manner after being reacted with (and agglutinated by) quinidine and antibody in the absence of complement. The Coombs test was negative even when the erythrocyte washings were performed in quinidine solution.

It is possible that more gentle handling of the antigen-antibody-hapten combination might have permitted maintenance of the loose bond. From the observations described we infer that the marked *in vitro* instability of the presumed complex is perhaps related to the extreme rarity of clinical hemolytic anemia due to quinidine.

As is known, sedormid induction of thrombocytopenic purpura is an uncommon but by no means rare event. Hemolytic anemia due to quinidine must be extremely rare, since no previous case has been reported. It may be pertinent to the relative incidences of these reactions that the presumed platelet-sedormid-antibody is a very loose one (as suggested by Ackroyd) and that the presumed erythrocyte-quinidine-antibody combination is even looser, as suggested by our data. The most reasonable immunologic mechanism to explain our experimental data, and one which is consistent with although not proved by our findings, is the development in rare individuals of antibodies against an erythrocyte-quinidine combination wherein the drug acts as a hapten essential for the reaction and not by "damaging" the red blood cell and rendering it antigenic *per se*.

#### SUMMARY

A case is described in which the therapeutic administration of quinidine sulfate was associated with the acute occurrence of both thrombocytopenic purpura and hemolytic anemia. Both processes subsided within approximately one week following withdrawal of the drug.

Immune mechanisms were demonstrated both in relation to the thrombocytopenic purpura and to the hemolytic anemia, and detailed studies



relative to the latter process are presented in this paper. The following observations were made: (1) The patient's serum contained a factor which, in the presence of quinidine, caused hemagglutination of all red cells tested, and which caused hemolysis when complement was present. (2) Blood concentrations of quinidine attained with therapeutic doses of the drug were capable of activating the hemolytic system. The levo-isomer of quinidine and other agents did not do so. (3) The serum factor was present in high concentration initially and a significant titer was still present 140 days after the clinical reaction. The factor was stable, migrated electrophoretically with gamma globulin and was adsorbed onto red blood cells in the presence of quinidine. Complement was required and was fixed in the lytic reaction. The serum factor was defined as an antibody and the hemagglutinating-hemolytic reactions as immunologic. (4) The combination of erythrocyte-quinidine-antibody was an extremely loose one, suggesting one possible explanation for the rarity of reports of hemolytic anemia due to quinidine.

It is suggested that hemolytic anemia and hematocytopenia may be shown to be due to other drugs by *in vitro* methods such as employed in this case, and thus spare the patient the obvious risk of a test dose or repeat course of the medication. Such studies may further elucidate the mechanisms of drug-induced and idiopathic immunocytopenias.

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Chancroid	Infestation
Colitis	Pneumonia
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Diphtheria	Q Fever
Dysentery, Amebic	Rocky Mountain Spotted Fever
Dysentery, Bacillary	Salpingitis
Empyema	Scarlet Fever
Endocarditis, Bacterial	Scrub Typhus
Epididymitis	Sepsis, Puerperal
Erysipelas	Septic Sore Throat
Furunculosis	Septicemia
Gangrene	Sinusitis
Gastroenteritis	Skin Graft Infections
Gonorrhea	Surgical Prophylaxis
Granuloma Inguinale	Tonsillitis
Klebsiella Pneumonia	Tracheobronchitis
Laryngitis	Tularemia
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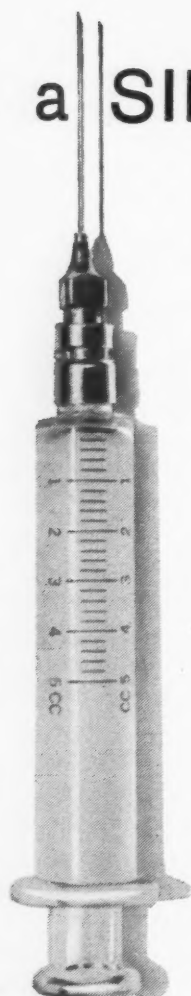
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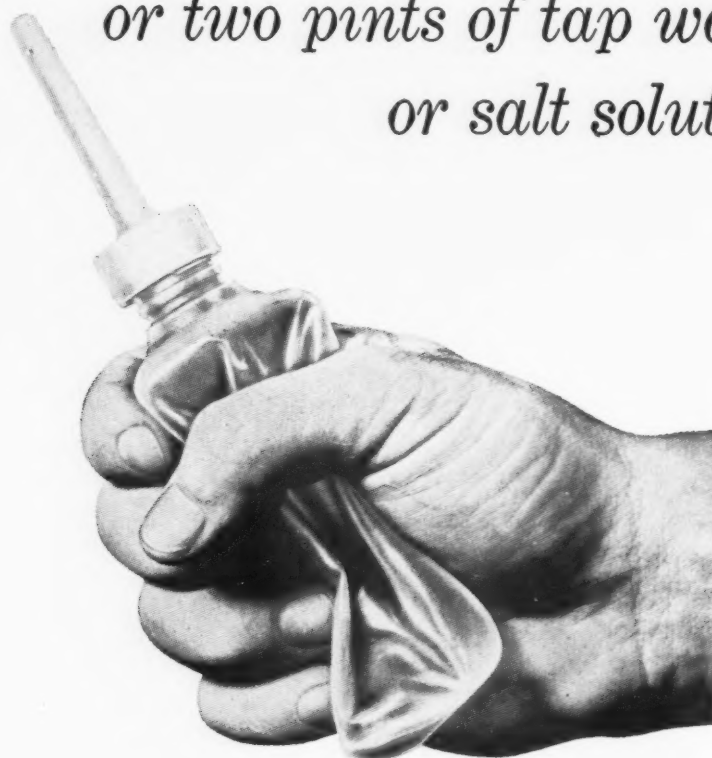
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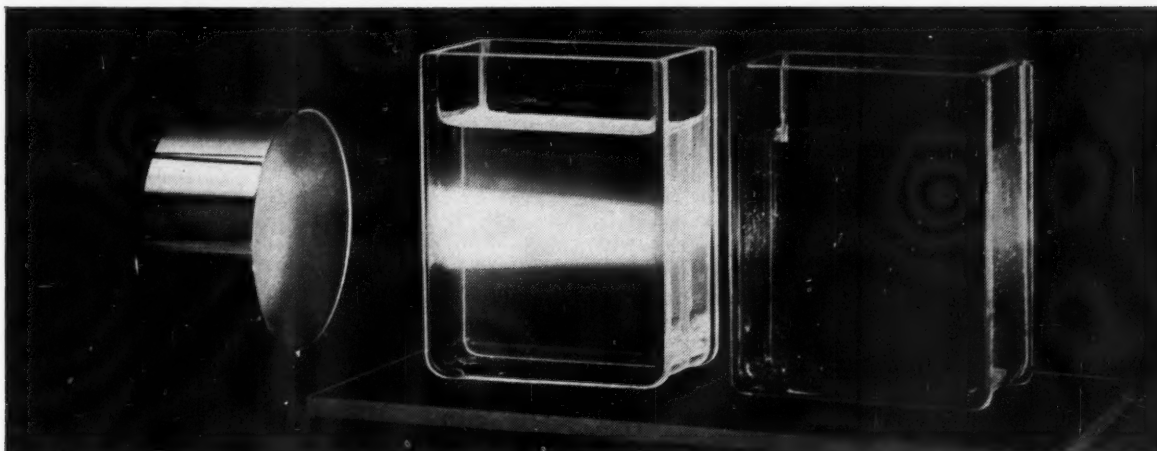
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**Bibliography:** 1. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, The Macmillan Company, 1952, p. 184. • 2. Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, p. 64/6. • 3. Ahrens, E. H., Jr., and Kunkel, H. G.: J. Exper. Med. 90:409 (Nov. 1) 1949.

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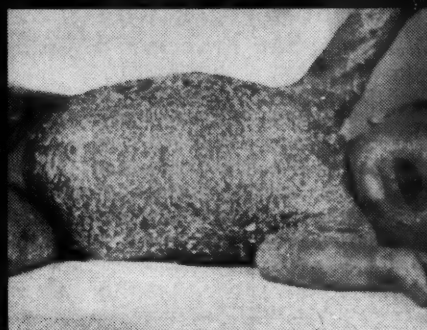
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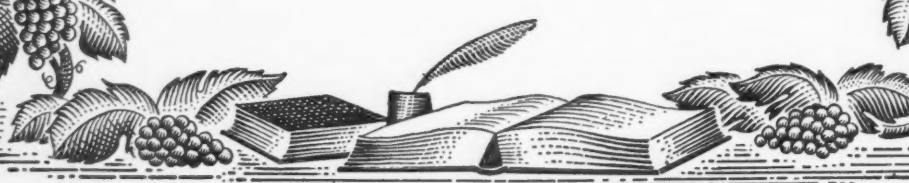
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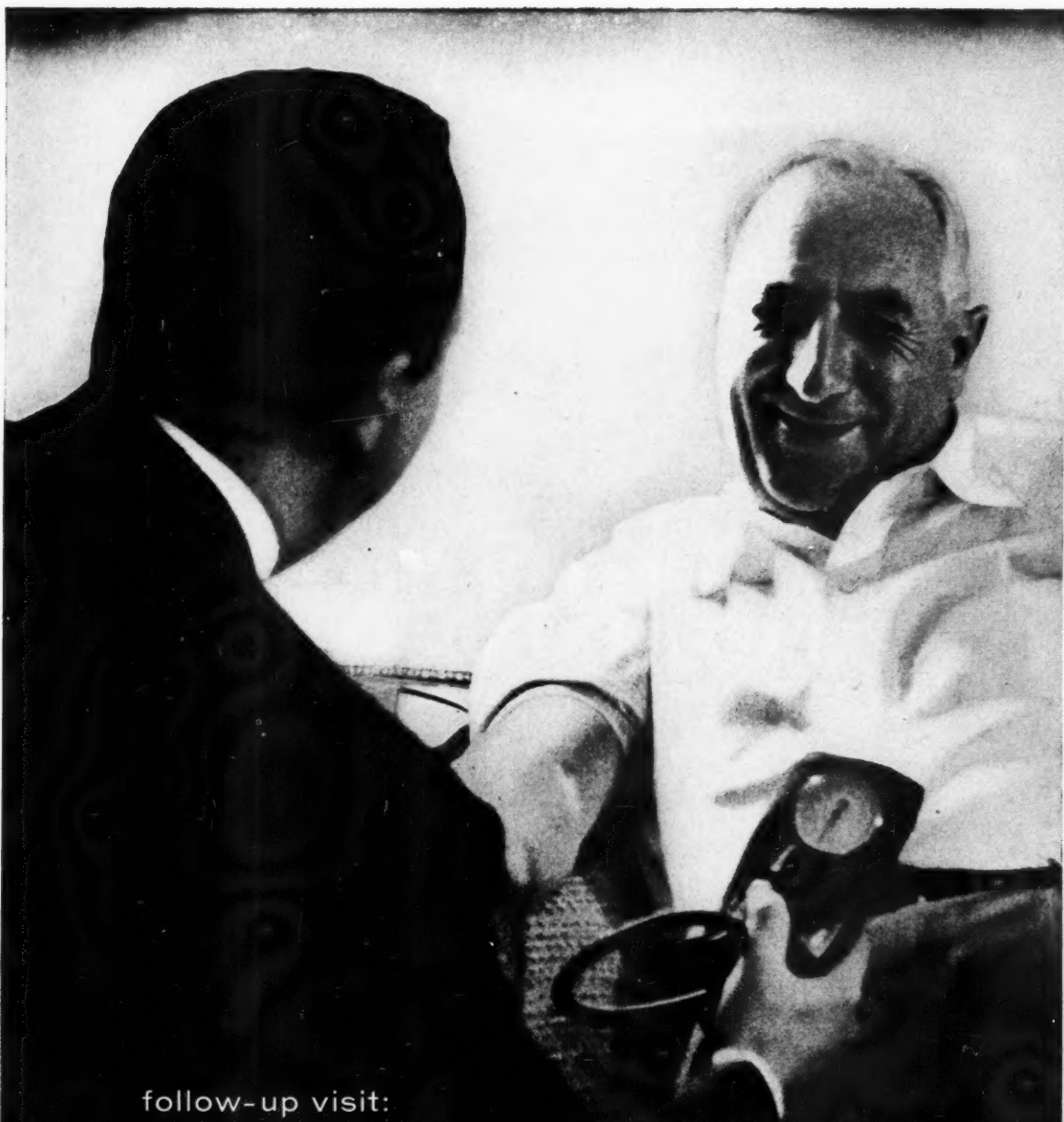
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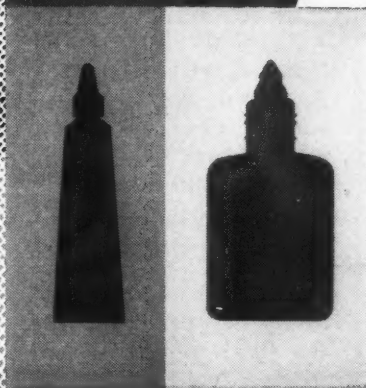
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Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129-35, 1955.

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Wood, J. E., Jr.; Beckwith, J. R., and Camp, J. L.: J.A.M.A. 159:635, 1955.

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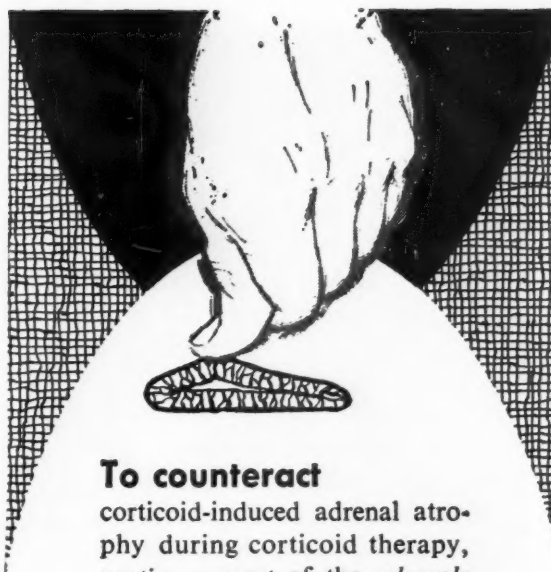


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—GARDNER, F. H.: J. LAB. & CLIN. MED. **41**:56 (JAN.) 1953.

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—HOLLY, R. G.: OBST. & GYNEC. **5**:562 (APRIL) 1955.

With Roncovite, . . . "most patients felt an increased sense of well-being when hemoglobin levels were elevated."

—HILL, J. M.; LAJOUS, J., AND SEBASTIAN, F. J.: TEXAS J. MED. **51**:686 (OCT.) 1955.

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One tablet after each meal and at bedtime. Children 1 year or over, 0.6 cc. (10 drops); infants less than 1 year, 0.3 cc. (5 drops) once daily diluted with water, milk, fruit or vegetable juice.

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without fear of overstimulation . . .*

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A HAPPY MEDIUM  
IN PSYCHOMOTOR  
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- *Boosts the spirits, relieves physical fatigue and mental depression . . . yet has no appreciable effect on blood pressure, pulse rate or appetite.*

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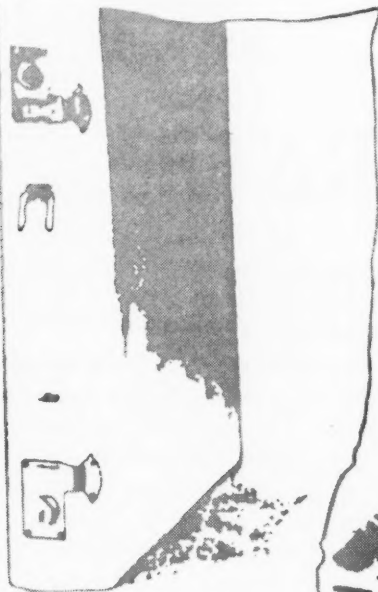
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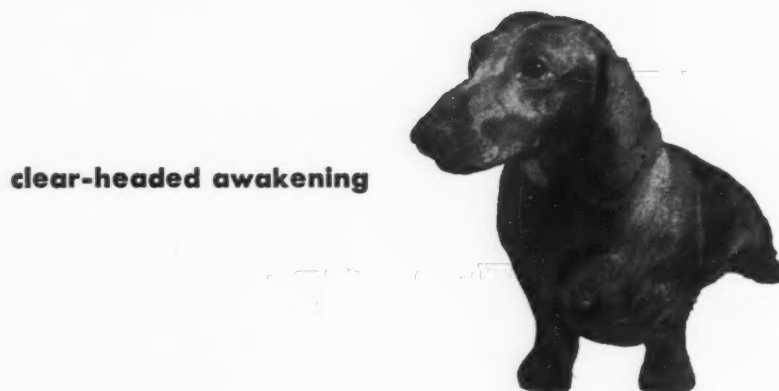
RITALIN® hydrochloride  
(methyl-phenidylacetate  
hydrochloride CIBA)

**References:** 1. Pocock, D. G.: Personal communication. 2. Harding, C. W.: Personal communication. 3. Hollander, W. M.: Personal communication.

**Supplied:** Tablets, 5 mg. (yellow) and 10 mg. (blue); bottles of 100, 500 and 1000. Tablets, 20 mg. (peach-colored); bottles of 100 and 1000.



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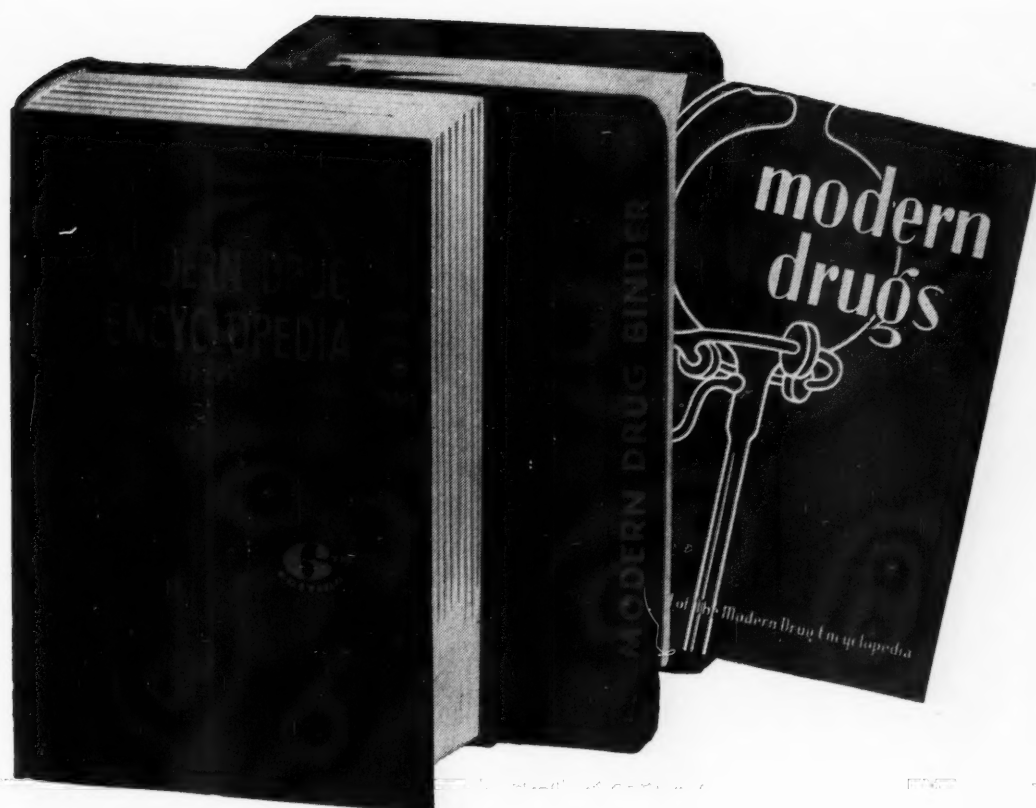
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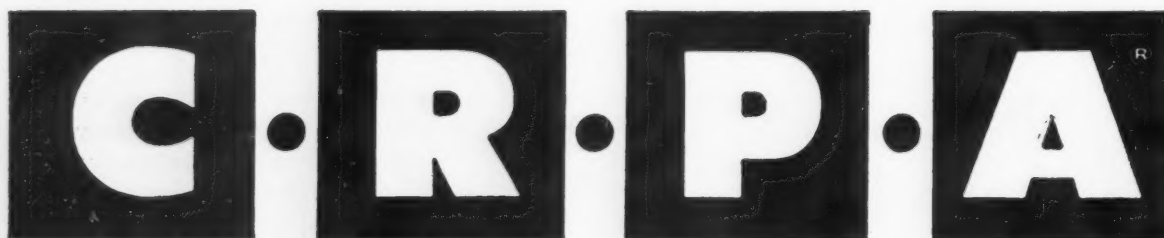
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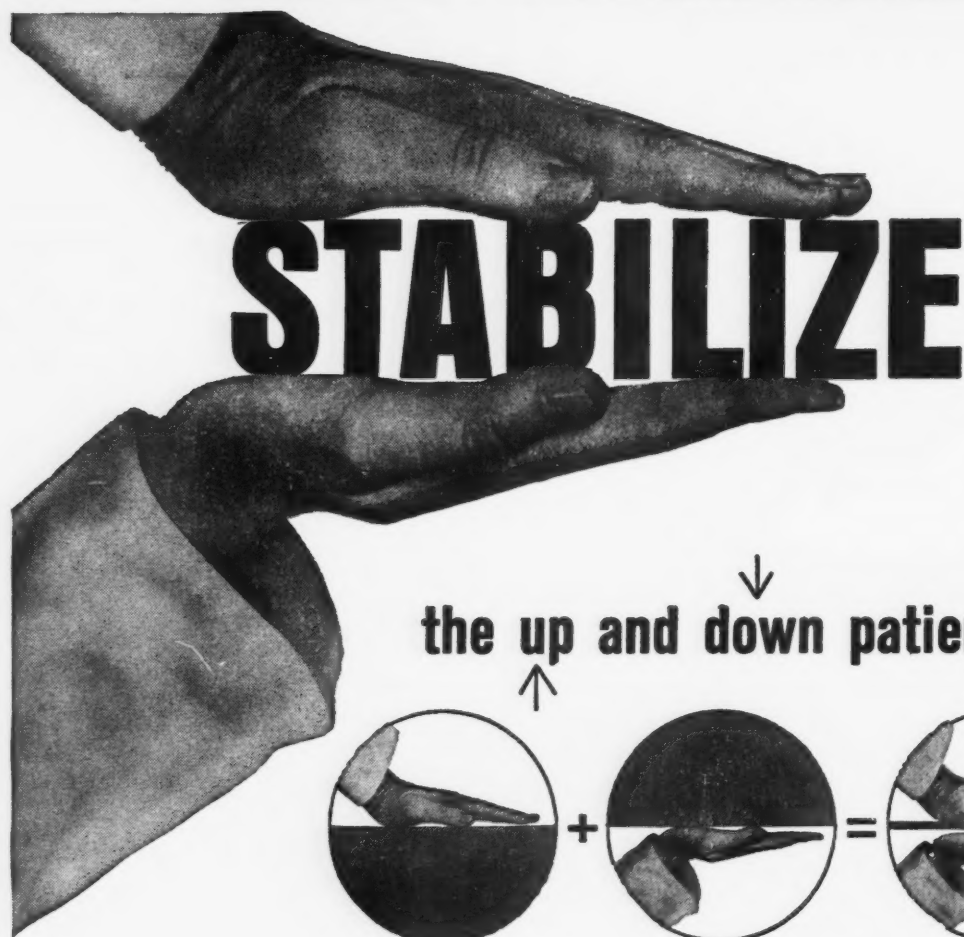
In Canada: William Solin Ltd.

1. Shackman, N. H., Heffer, E. T., and Kroop, I. G.: *Am. Heart J.* 48:599 (Oct.) 1954. • 2. Stollerman, G. H., and others: *Am. J. Med.* 15:645 (Nov.) 1953. • 3. McEwen, C.: *M. Clin. North America* 39:353 (March) 1955. • 4. Wood, H. F., and McCarty, M.: *Am. J. Med.* 17:768 (Dec.) 1954. • 5. McEwen, C., and Ziff, M.: *M. Clin. North America* (May) 1955, to be published.

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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